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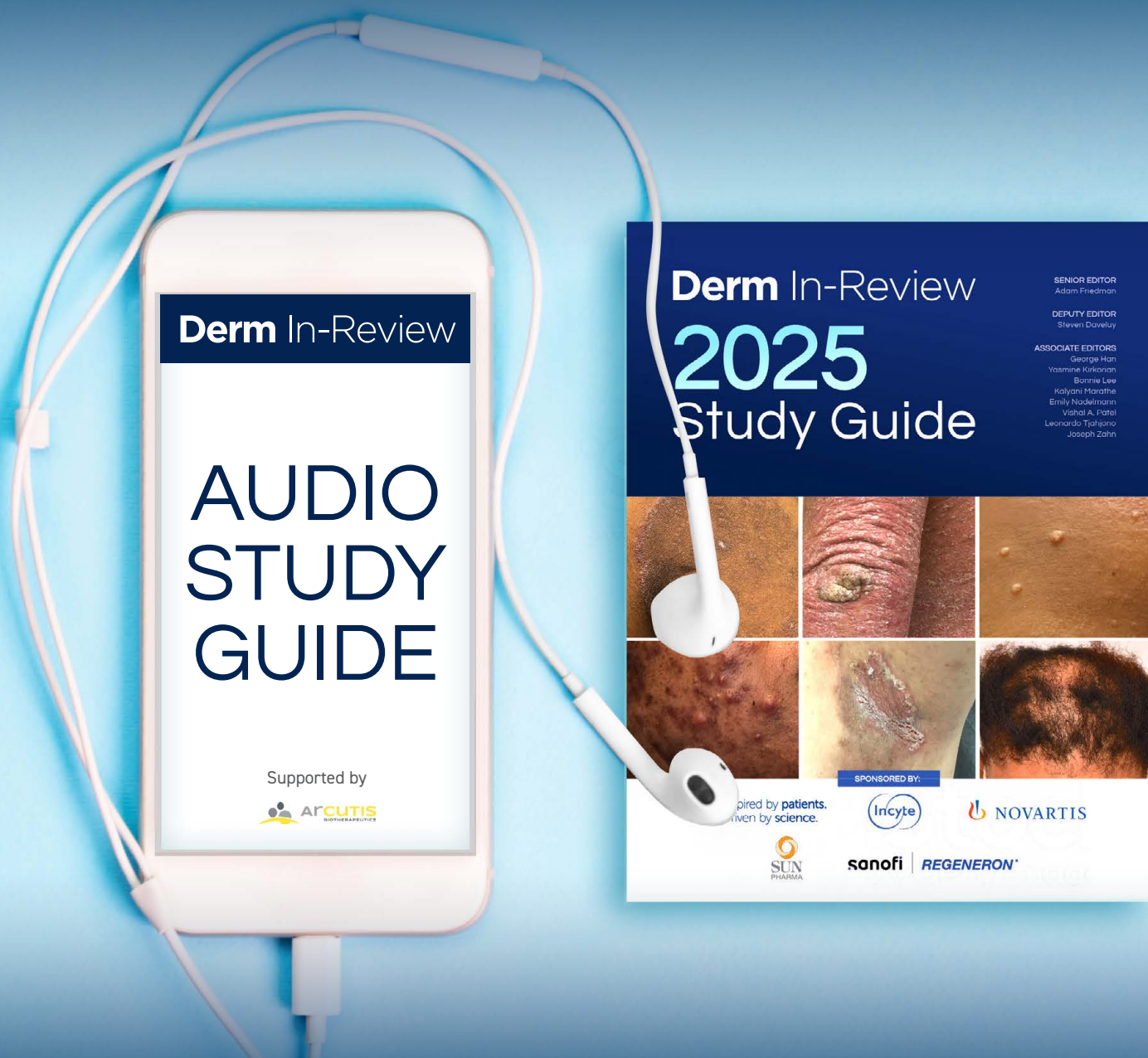
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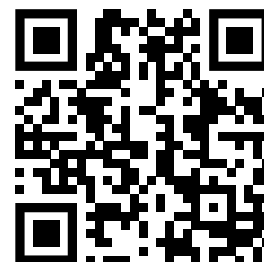
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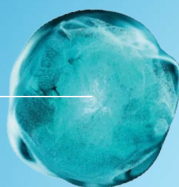


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# Remibrutinib: Insights Into Its Mechanism of Action and Use for Dermatologic Conditions

Joshua Burshtein MD,<sup>a</sup> Todd Schlesinger MD<sup>b</sup>

<sup>a</sup>Department of Dermatology, University of Illinois Chicago, Chicago, IL

<sup>b</sup>Clinical Research Center of the Carolinas, Charleston, SC

## ABSTRACT

**Objective:** Chronic spontaneous urticaria (CSU) is a chronic, debilitating condition characterized by recurrent wheals and/or angioedema. Several cytokines have been linked to CSU, including Bruton tyrosine kinase (BTK), providing the rationale for emerging targeted therapies. Remibrutinib is an oral, highly selective BTK inhibitor that is in clinical development for CSU as well as several other dermatologic diseases.

**Methods:** A comprehensive literature search was completed using the keywords “chronic spontaneous urticaria,” “pathogenesis,” “Bruton tyrosine kinase,” “remibrutinib,” and “mechanism of action.” The authors reviewed all studies and included those that addressed the topic of the review.

**Results:** Remibrutinib has completed phase 3 trials for the treatment of CSU. Remibrutinib-treated patients experienced a significantly greater decrease in 7-day Urticaria Activity Score at week 12 compared to placebo in REMIX-1 (-20.0 remibrutinib vs -13.8 placebo,  $P < 0.001$ ) and REMIX-2 (-19.4 remibrutinib vs -11.7 placebo,  $P < 0.001$ ). Clinically meaningful effects were seen after one week. The rate of adverse effects was similar between remibrutinib and placebo groups. Remibrutinib is also being evaluated in clinical trials for hidradenitis suppurativa, with a phase 2 clinical trial reporting 72.7% of remibrutinib-treated patients with 25 mg twice daily achieved simplified HS clinical response score vs 34.7% in the placebo group.

**Limitations:** This is a review article and is limited by the information available in the published literature. In addition, comparison between studies is limited as varying methodologies were used.

**Conclusion:** BTK inhibitors are promising therapeutic candidates given their central role in multiple inflammatory pathways and the pathogenesis of diverse immunologic disorders. Remibrutinib has demonstrated clinical efficacy for the treatment of CSU with an acceptable safety profile.

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## INTRODUCTION

Chronic spontaneous urticaria (CSU) is a chronic, debilitating condition characterized by recurrent wheals and/or angioedema.<sup>1</sup> Symptoms occur daily or nearly daily for at least 6 weeks, with angioedema reported in up to 50% of patients without an identifiable external trigger.<sup>1-3</sup> The disease affects approximately 0.5% to 1% of the general population, with a higher prevalence in women, and most commonly presents between 20 and 40 years of age.<sup>2</sup> For the majority of patients, CSU persists for 1 to 5 years, although cases with more severe disease may last longer, contributing substantially to impaired quality of life.<sup>2</sup>

The pathogenesis of CSU is predominantly mediated by mast cell degranulation, though the exact mechanisms by which mast cells are activated are not completely known.<sup>4</sup> Additional contributions are from eosinophils and basophils, which release vasoactive mediators involved in urticaria.<sup>1,5,6</sup> A wide range of cytokines and chemokines have been linked to CSU, providing the rationale for emerging targeted therapies.<sup>5</sup>

Bruton tyrosine kinase (BTK), a member of the TEC family of cytoplasmic protein tyrosine kinases, is expressed across multiple cell types and forms part of the signal transduction of mast cell degranulation.<sup>7,8</sup> Targeting of BTK has been explored for the treatment of several B-cell driven diseases, leading to approval by the Food and Drug Administration (FDA) for therapies such as ibrutinib, acalabrutinib, and zanubrutinib.<sup>9-11</sup> Given the role of BTK in the pathogenesis of CSU, there is increasing literature demonstrating the efficacy of BTK inhibition for the treatment of this disease.

### Existing Therapeutic Options for Chronic Spontaneous Urticaria

First-line therapeutic options for CSU are second-generation H<sub>1</sub>-antihistamines.<sup>12</sup> These include bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine.<sup>12</sup> However, >50% of patients who receive this treatment continue to experience symptoms of CSU and 75% have sustained symptoms despite increasing dosage up to 4 times the standard dose.<sup>13-16</sup> For individuals who are not controlled

with H<sub>1</sub>-antihistamines, the addition of the anti-IgE agent omalizumab has been recommended.<sup>12</sup> A meta-analysis reported that of 12 randomized controlled trials, patients treated with omalizumab achieved a 7-day Urticaria Activity Score (UAS7) <6 at a significantly higher rate compared to placebo, as well as significantly reducing UAS7, itch severity score (ISS), and hive count.<sup>17</sup> Recently, dupilumab, which blocks interleukin (IL)-4 and IL-13, received Food and Drug Administration (FDA) approval for treatment of CSU in those aged ≥12 years who are not adequately controlled by H<sub>1</sub>-antihistamines.<sup>18</sup> In two phase 3 clinical trials, dupilumab significantly reduced UAS7, and in one of the trials, also improved ISS.<sup>19</sup> Other treatments that have a lower efficacy and/or lower quality evidence for CSU that are not routinely recommended include cyclosporine, doxepin, methotrexate, montelukast, and dapsone.<sup>12</sup>

#### Remibrutinib: Mechanism of Action

BTK is a cytoplasmic protein tyrosine kinase of the TEC kinase family that is expressed in a wide variety of cells in both the adaptive and innate immune systems such as B-cells, macrophages, mast cells, and others.<sup>20–22</sup> It is not expressed in mature plasma cells and T-cells.<sup>23</sup> BTK has a primary role in B-cell receptor signaling and is a downstream effector for signaling through pro-inflammatory FcεRI (an IgE receptor).<sup>20–22,24</sup> BTK inhibition in vitro has been associated with reduction of mediator release in basophils and decreased IgE-mediator degranulation and cytokine production in human mast cells.<sup>11,25</sup>

Remibrutinib (Rhapsido®, Novartis Pharmaceuticals Corp., East Hanover, NJ) is the only FDA-approved oral, highly selective BTK inhibitor.<sup>26</sup> It covalently binds to inactive BTK to suppress the downstream cascade and activation of granule mediators including histamine and proinflammatory cytokines, and therefore prevents mast cell degranulation.<sup>23,27</sup> Treatment with remibrutinib markedly reduces CD63+ mast cells (a marker for mast cell activation and degranulation) and nearly eliminates basophil activity triggered by FcεR1 activation.<sup>28</sup> Notably, one study found that remibrutinib inhibits mast cells and basophils independent of baseline FcεR1 expression and omalizumab response.<sup>28</sup>

Literature has demonstrated the selective and potent binding of remibrutinib to BTK while only minimal partial binding to other kinases (eg, TEC, BMX).<sup>23</sup> On the other hand, other BTK inhibitors, ibrutinib and branebrutinib, showed similar high affinity for BTK but had poorer selectivity, binding to other kinases (BMX, TEC, EGFR, ERBB2, and ERBB4) at high levels as well.<sup>23</sup> BTK inhibitors acalabrutinib, tirabrutinib, and evobrutinib had lower potent binding to BTK and were less selective compared to remibrutinib.<sup>23</sup> Through in vitro analyses, remibrutinib was found to have strong BTK inhibition starting from the earliest time-point with no time-dependent shift in concentration. In human blood, it further showed rapid covalent binding to cellular BTK, which was faster than all other covalent BTK inhibitors except branebrutinib.<sup>23</sup>

#### Summary of Clinical Development

##### *Chronic Spontaneous Urticaria*

Remibrutinib has been studied in multiple clinical trials. In a phase 1 randomized clinical trial, remibrutinib is effective in preventing basophil activation in ex vivo assays.<sup>27</sup> It demonstrated almost complete blood BTK occupancy and near complete basophil or skin prick test inhibition at various dosages.<sup>27</sup> It was well-tolerated at all doses examined, and there was no dose-limiting toxicity reported.<sup>27</sup>

A randomized, double-blind, placebo-controlled phase 2b dose-finding trial evaluated patients treated with remibrutinib over 12 weeks.<sup>29</sup> The patient population consisted of those who were inadequately controlled with second-generation H<sub>1</sub>-antihistamines and had moderately active CSU (with or without prior anti-IgE treatment).<sup>29</sup> Of the 311 patients randomized in this trial, there was a reduced UAS7 for all remibrutinib doses from week 1 until week 12.<sup>29</sup> Least-squares mean change from baseline at week 4 was -19.1 (10 mg once daily), -19.1 (35 mg once daily), -14.7 (100 mg once daily), -16.0 (10 mg twice daily), -20.0 (25 mg twice daily), -18.1 (100 mg twice daily), and -5.4 for placebo (*P*<0.0001 for all doses vs placebo).<sup>29</sup> The 25 mg twice-daily group had the most effectiveness, with 41.9% achieving UAS7=0 and 55.8% achieving UAS7 ≤6 at week 12 (vs 14.3% and 28.6% with placebo, respectively).<sup>29</sup> Clinically meaningful improvements were observed as early as week 1 and maintained until week 12.<sup>29</sup> Previous treatment with anti-IgE agents did not affect the change in UAS7 score.<sup>29</sup> Regarding safety profile, 58.1% of patients receiving remibrutinib had at least 1 adverse event (AE), with the majority being mild.<sup>29</sup> The most common AEs were infections (24.0% remibrutinib vs 21.4% placebo) and skin/subcutaneous disorders (16.9% remibrutinib vs 4.8% placebo).<sup>29</sup> Serious AEs occurred in 1.9% (5/267) of patients who received any dose of remibrutinib.<sup>29</sup> Of these, only two were suspected to be related to treatment.<sup>29</sup>

Long-term efficacy and safety up to 52 weeks were evaluated in a phase 2b extension trial. Patients who had UAS7 ≥16 at the start of the extension period received remibrutinib 100 mg twice daily for 52 weeks.<sup>30</sup> At week 52, mean change from baseline UAS7 was -21.8, UAS7=0 was achieved in 55.8% of patients, and UAS7 ≤6 was achieved in 68.0% of patients.<sup>30</sup> This study reported a comparable safety profile to the phase 2b core trial.<sup>30</sup> The most common treatment-emergent adverse events (TEAEs) were infections (30.9%, skin/subcutaneous tissue (26.8%), and gastrointestinal disorders (16.5%), which are frequently present in patients with CSU.<sup>30–32</sup> Most TEAEs were mild to moderate and deemed unrelated to remibrutinib, while only 11.9% had at least one TEAE that was deemed possibly associated with remibrutinib.<sup>30</sup> Severe AEs occurred in 4.1% of patients, and 5.7% discontinued remibrutinib due to a TEAE.<sup>30</sup>

Remibrutinib completed phase 3 trials in identical, multicenter, double-blind, randomized, placebo-controlled REMIX-1 and REMIX-2.<sup>33</sup> Both trials enrolled a similar number of patients:

REMIX-1: 313 remibrutinib vs 157 placebo and REMIX-2: 300 remibrutinib vs 155 placebo.<sup>33</sup> The remibrutinib group experienced significantly greater decrease in UAS7 at week 12 compared to placebo in REMIX-1 (-20.0 remibrutinib vs -13.8 placebo,  $P<0.001$ ) and REMIX-2 (-19.4 remibrutinib vs -11.7 placebo,  $P<0.001$ ).<sup>33</sup> Similar to prior trials, these changes occurred as early as week 1.<sup>33</sup> The effects were maintained through week 24.<sup>33</sup> Further, significantly more patients treated with remibrutinib achieved UAS7  $\leq 6$  at week 12 compared to placebo [REMIX-1, 49.8% vs 24.8% ( $P<0.001$ ) and REMIX-2, 46.8% vs 19.6% ( $P<0.001$ )].<sup>33</sup> Remibrutinib-treated patients also achieved UAS7=0 at a significantly higher rate [REMIX-1, 31.1% vs 10.5% ( $P<0.001$ ); REMIX-2, 27.9% vs 6.5% ( $P<0.001$ )].<sup>33</sup> Rates of AEs and serious AEs were consistent with prior trials and were similar between remibrutinib and placebo groups.<sup>33</sup>

A systematic review/meta-analysis recently explored the efficacy and safety of systemic treatments for CSU. The study reported that standard-dose omalizumab (300 mg every 4 weeks) and remibrutinib were among the most effective therapies for improving patient-important outcomes.<sup>34</sup> Standard-dose omalizumab was found to have a UAS7 mean difference (MD) of -8.37 [Grading of Recommendations Assessment, Development and Evaluation (GRADE) level: high certainty], remibrutinib had a UAS7 MD of -7.65 (GRADE: high certainty), and dupilumab had a UAS7 MD of -6.01 (GRADE: moderate certainty).<sup>34</sup> Further, standard-dose omalizumab and remibrutinib had the highest effect on the percentage of angioedema-free weeks (MD 8.75% more and MD 15.00% more, respectively; both GRADE: high certainty).<sup>34</sup> These two therapies also had the greatest impact on urticaria-related quality of life. On the Chronic Urticaria Quality of Life Questionnaire, standard-dose omalizumab (MD -12.68, GRADE: high certainty) and remibrutinib (MD -11.65, GRADE: high certainty), had the greatest improvement.<sup>34</sup>

#### *Hidradenitis Suppurativa*

Hidradenitis Suppurativa (HS) is a chronic, inflammatory skin disease characterized by painful nodules, abscesses, draining tunnels, and scarring.<sup>35</sup> Remibrutinib is being evaluated to treat HS. In a phase 2 clinical trial, after 16 weeks of treatment, 72.7% of patients who received remibrutinib 25 mg twice daily achieved simplified HS clinical response score (sHiSCR;  $\geq 50\%$  decrease in abscess and inflammatory nodule count, without increase in draining tunnels compared to baseline) vs 48.5% who received 100 mg twice daily and 34.7% in the placebo group.<sup>36</sup> Improvements were identified as early as week 2.<sup>36</sup> Additionally, patients in the remibrutinib 25 mg and 100 mg groups achieved greater HiSCR75 (42.4% and 27.3% vs 18.4%) and HiSCR90 (36.4% and 15.2% vs 8.2%) compared to placebo.<sup>36</sup> Frequency of AEs was similar between the groups.<sup>36</sup> Phase 3 clinical trials are currently ongoing.

#### **Future Directions**

Given the mechanism of action of remibrutinib, there is a great potential for its utilization in a variety of diseases. Literature has shown the presence of increased expression of BTK in B cells of patients with autoimmune diseases.<sup>37–39</sup> In fact, there may be a correlation of BTK levels and antibody production.<sup>37,38</sup>

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease affecting millions of individuals worldwide.<sup>40</sup> There are several systemic therapies available for patients with moderate-to-severe AD, including biologics and Janus kinase (JAK) inhibitors. However, there remains a challenge for many patients to adequately control the symptoms of AD. There is increasing evidence that B cells, mast cells, and basophils play a role in the pathogenesis of inflammation in AD.<sup>41,42</sup> Recently, an oral, reversible covalent BTK inhibitor, rilzabrutinib, was assessed in a phase 2 proof-of-concept clinical trial for treatment of moderate-to-severe AD in patients with inadequate response to topical corticosteroids.<sup>43</sup> The primary endpoint, which was percentage change in Eczema Area and Severity Index (EASI) score from baseline to week 16, did not reach statistical significance.<sup>43</sup> There was, however, a rapid improvement in absolute and relative change in weekly average of the daily Peak Pruritus Numerical Rating Scale.<sup>43</sup> Rilzabrutinib was well tolerated with mostly mild TEAEs.<sup>43</sup> Additional development and clinical evaluation are required to thoroughly assess the potential efficacy and safety of BTK inhibitors for treatment of AD.

Rilzabrutinib is also under investigation as a treatment for CSU.<sup>44</sup> In a phase 2 clinical trial (RILECSU), patients experienced significant reduction from baseline in weekly Itch Severity Score (ISS7) (least squares [LS] mean, -9.21 vs -5.77; difference, -3.44,  $P=0.02$ ) and UAS7 (LS mean, -16.89 vs -10.14; difference, -6.75,  $P=0.02$ ) when treated with rilzabrutinib 1200 mg per day compared to placebo.<sup>44</sup> Improvements in ISS7, UAS7, weekly Hives Severity Score (HSS7) and weekly Angioedema Activity Score (AAS7) were observed by week 1.<sup>44</sup> Rilzabrutinib had an overall favorable risk-benefit profile, with most frequent TEAEs including diarrhea, nausea, headache, and abdominal pain.<sup>44</sup>

Moreover, by inhibiting IgE-mediated signaling, BTK inhibitors can interrupt the cascade of events that trigger allergic reactions, highlighting their potential for treating food allergies (FA).<sup>45</sup> One phase 2 open-label study analyzed 10 adults with peanut allergy treated with BTK inhibitor acalabrutinib.<sup>46</sup> After treatment, the median tolerated dose of peanut protein increased from 29 mg at baseline to 4044 mg, and 7/10 participants were able to consume the maximum protocol dose (4044 mg) without any adverse reactions.<sup>46</sup> The other three patients experienced a 32- to 217-fold increase in peanut tolerance, demonstrating a strong desensitization effect.<sup>46</sup> In addition, a humanized mouse model found that pretreatment with two oral doses of acalabrutinib

hours before allergen exposure prevented moderate-to-severe anaphylaxis, stressing their potential for acute intervention.<sup>47</sup> Larger placebo-controlled trials are needed to confirm and define the role of BTK inhibitors in the management of FA.

Pemphigus is a group of autoantibody-driven skin diseases characterized by blisters and erosions of the skin and/or mucous membranes.<sup>48</sup> Pemphigus is due to IgG autoantibodies that act against desmoglein 1 and 3 adhesion molecules in the epidermis.<sup>48</sup> Currently, treatment of pemphigus involves immunosuppressive medications consisting of systemic corticosteroids and rituximab. These therapies have substantial adverse effects associated with their usage and although they can be beneficial, there is an unmet need for targeted treatment with improved safety profile. Due to the mechanism of action, BTK inhibitors are being evaluated for treatment of pemphigus.<sup>49</sup> Rilizabrutinib was assessed in a phase 2 clinical trial for pemphigus vulgaris and 52% of patients achieved the primary endpoint (absence of new lesions and healing of existing lesions).<sup>50</sup> In a phase 3 clinical trial for treatment of pemphigus, however, the results did not meet their primary or key secondary endpoints, including complete remission from weeks 29 to 37 with minimal doses of corticosteroids ( $\leq 10$  mg day).<sup>51</sup> Another selective BTK inhibitor, tirabrutinib, was evaluated in a phase 2 clinical trial.<sup>52</sup> After 52 weeks of treatment, 50.0% of patients had complete remission and 14.3% had partial remission. There was no correlation between tirabrutinib and serious AEs, though 87.5% of patients reported any AE.<sup>51</sup>

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease that can affect many different organ systems including the heart, skin, kidney, nervous system and others.<sup>53</sup> The pathogenesis of SLE is due to dysregulation of immune system components producing autoantigens and antinuclear antibodies and depositing immune complexes.<sup>53</sup> The skin is the second most commonly affected organ by SLE.<sup>54</sup> Literature has discovered that various aspects of the BTK signaling pathway are altered in B cells in SLE and BTK inhibitors are being explored as a potential therapeutic option for patients with cutaneous, renal, and articular manifestations of SLE.<sup>11,55</sup>

Alopecia areata (AA) is an autoimmune disease characterized by non-scarring hair loss.<sup>56</sup> AA can be localized as small patches on the scalp and/or body and can progress to total loss of hair on the scalp and/or the body.<sup>56</sup> The pathogenesis includes IgG antibodies against hair follicle cells.<sup>56</sup> Over the past several years, novel therapeutic options have become available for treatment of AA, including JAK inhibitors such as baricitinib and ritlecitinib.<sup>57</sup> Baricitinib is a selective, reversible JAK1 and JAK2 inhibitor, while ritlecitinib is a selective, irreversible JAK3 and TEC kinase inhibitor.<sup>57</sup> Ritlecitinib's effect on TEC kinases is primarily achieved through inhibition of interleukin-2-inducible

T-cell kinase, and targeting this molecule may enable attenuation of the inflammation present in AA.<sup>58</sup> In fact, one mouse study found that selective ITK inhibition had a partial effect on AA prevention and reversal.<sup>59</sup> Vitiligo, an autoimmune depigmenting disease, is another condition that has demonstrated improvements with inhibition of JAK3/TEC.<sup>60,61</sup> However, it is unclear how much of this effect comes from inhibition of BTK compared to JAK3 and other TEC kinases. Targeted BTK inhibition could enable more selective treatment of alopecia areata and vitiligo, though additional studies are needed to explore this potential.

In addition to dermatologic diseases, remibrutinib has demonstrated efficacy in reducing neuroinflammation in preclinical models of multiple sclerosis (MS). One study found that remibrutinib inhibited B-cell-dependent human myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis mouse models for MS.<sup>62</sup> It did not reduce B cells, total immunoglobulin levels or myelin oligodendrocyte glycoprotein-specific antibody response.<sup>62</sup> Studies on the treatment of MS with BTK inhibitors are ongoing.

## CONCLUSION

BTK inhibitors are promising therapeutic candidates given their central role in multiple inflammatory pathways and the pathogenesis of diverse immunologic disorders. These agents, such as remibrutinib, can provide improved specificity and tolerability compared to existing treatments for various dermatologic diseases due to minimized off-target activity. Remibrutinib has demonstrated efficacy for CSU in multiple clinical trials and has the potential to revolutionize management of this difficult-to-treat disease. Ongoing research is directed toward evaluating its utility across a range of dermatologic diseases.

## DISCLOSURES

Joshua Burshtein has no conflicts. Todd Schlesinger serves as a consultant, investigator, speaker and/or advisor for Abbvie, Ammiral, Allergan (An Abbvie company), ASLAN, Arcutis, Biofrontera, Beiersdorf, Benev, Bristol-Myers Squibb, Castle Biosciences, Dermsquared, Galderma, Eli Lilly, ExoCoBio, Incyte, Janssen, LEO, L'Oreal, Medicus, Novartis, Pfizer, RBC Consultants, Regeneron, Sanofi, Sun Pharma, Takeda, UCB, and Verrica and receives a salary from Avant Health.

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AUTHOR CORRESPONDENCE

Joshua Burshtein MD

E-mail:..... jburshtein13@gmail.com

# Racial and Ethnic Representation in Clinical Trials of Janus Kinase Inhibitors for Dermatologic Conditions: A Systematic Review

Christine Olagun-Samuel BA,<sup>a\*</sup> Maame-Afua Ansah BA,<sup>b\*</sup> Purvi Shakelly BS,<sup>b</sup> Nabiha Sherali BA,<sup>b</sup> Aminat Ologunebi BS,<sup>c</sup> Kristen Lo Sicco MD,<sup>a</sup> Prince Adotama MD<sup>a</sup>

<sup>a</sup>Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine, New York, NY

<sup>b</sup>Rutgers New Jersey Medical School, Newark, NJ

<sup>c</sup>American University of the Caribbean School of Medicine, Cupecoy, Saint Maarten

\*Each of these authors contributed equally

## ABSTRACT

**Background:** Janus kinase (JAK) inhibitors represent promising therapies for dermatologic conditions, including psoriasis, hidradenitis suppurativa (HS), atopic dermatitis (AD), systemic lupus erythematosus (SLE), and vitiligo. There are little data available evaluating the composition of research cohorts for this emerging treatment modality. Adequate racial representation in clinical trials is essential.

**Objective:** To characterize the study populations of clinical trials for Janus kinase inhibitors for dermatologic indications.

**Methods:** Clinical trials were identified from January 2000 to March 2025 through PubMed using the following keywords: “Janus kinase inhibitor,” “JAK inhibitor,” “alopecia areata,” “atopic dermatitis,” “hidradenitis suppurativa,” “systemic lupus erythematosus,” “systemic sclerosis,” “psoriasis,” and “vitiligo.” Additional trials were retrieved from ClinicalTrials.gov using the search term “JAK inhibitor.” Each trial was reviewed for demographic data, including race and ethnicity. Additional variables collected included Fitzpatrick skin type and quality-of-life measures. The distribution of race among trial participants was compared to the current US population and the condition-specific prevalence data where available.

**Results:** Of 399 identified studies, 207 clinical trials were included in our analysis, including 57,112 study participants were analyzed. Among studies reporting race (57.5%), representation was predominantly White (75.1%), followed by Asian (13.2%), Black (6.6%), American Indian/Alaska Native (0.48%), Native Hawaiian (0.11%), and multiple races (0.43%). Underrepresentation was pronounced among Black participants in psoriasis (1.3%), SLE (1.0%), and vitiligo trials (5.1%), although higher in HS (27.9%). Representation in these trials significantly differed from the racial distribution of US patients with vitiligo ( $P=0.012$ ) and AD ( $P=0.00088$ ). White patients were overrepresented in vitiligo and AD trials (Pearson residual=1.06, 2.71), while Black patients were underrepresented in these trials (Pearson residual=-2.66, -2.14). Additionally, a minority of studies (28.98%) reported on QoL metrics, which are essential tools for measuring disease burden and impact on patients.

**Conclusion and Relevance:** Reporting on racial data, Fitzpatrick skin type, and quality of life measures is lacking in clinical trials for Janus kinase inhibitors. These factors play a key role in addressing comorbidities and mitigating disease burden. These findings highlight a need for improved recruitment strategies targeting underrepresented populations in dermatologic clinical research.

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## INTRODUCTION

Increasingly, therapeutic advancements in dermatology favor targeted modalities, such as monoclonal antibodies and biologic therapies, which specifically address inflammatory cytokines, offering alternatives to broader immunosuppressive treatments.<sup>1,2</sup> Janus kinase (JAK) inhibitors represent a more recent therapeutic innovation for dermatologic disease, with FDA approvals for alopecia areata, vitiligo, and atopic dermatitis.<sup>3,4</sup> These agents modulate intracellular signaling through the JAK-STAT pathway, involved in inflammation

and autoimmune pathogenesis, offering promising treatment options for dermatologic conditions disproportionately affecting patients of color.<sup>5</sup>

In recent years, several JAK inhibitors have received regulatory approval for dermatologic indications. Baricitinib was approved by the United States Food and Drug Administration (FDA) in 2022 as the first systemic therapy for alopecia areata, representing a major advance in managing this autoimmune condition.<sup>6</sup> Topical ruxolitinib has been approved for both

atopic dermatitis and non-segmental vitiligo, expanding non-steroidal options for patients with inflammatory and pigmentary disorders.<sup>7-10</sup> These conditions are not only immune-mediated but also disproportionately affect patients with skin of color.<sup>11</sup> Atopic dermatitis, for example, is more prevalent and often more severe among Black and Hispanic pediatric patients, contributing to increased disease burden and reduced quality of life.<sup>12-15</sup> This holds true in both American and European contexts.<sup>13</sup> Incidence of severe atopic dermatitis in Black pediatric patients is sixfold greater than observed in their White counterparts.<sup>13</sup> Notably, atopic dermatitis presents differently in this population, with a study finding Black patients presenting with distinct clinical features such as more frequent hyperpigmented and violaceous lesions, and up to 70.3% of patients having perifollicular eruptions on extensors of joints.<sup>16</sup> Vitiligo can be more visibly distressing in patients with darker skin and is associated with heightened psychosocial impact.<sup>17,18</sup> Likewise, hidradenitis suppurativa is linked to limited healthcare utilization in Black patients, but high hospitalization risk despite being more common in Black patients.<sup>19</sup> Black patients have a relative risk of 2.86 for HS-related ED visits compared to White patients, likely linked to limited access to specialty care, delayed diagnosis, and consequently progression to more severe disease.<sup>20,21</sup>

Despite the elevated burden of these diseases among racially and ethnically diverse populations, clinical trials investigating dermatologic therapies frequently lack representative inclusion.<sup>22</sup> A recent analysis of dermatology clinical trials registered between 2017 and 2021 found persistent underrepresentation of Black, Hispanic, and Indigenous populations relative to disease prevalence.<sup>22</sup> Furthermore, a review of studies conducted between 2008 and 2022 found that Black individuals comprised more than 50% of enrolled participants in only two dermatologic disease categories (keloids and seborrheic dermatitis) despite a higher burden across multiple conditions.<sup>23</sup> This underrepresentation may prove consequential in diseases where clinical phenotype, treatment response, and outcomes may vary by race, ethnicity, and Fitzpatrick skin type.

This systematic review of dermatology literature assesses the racial and ethnic composition of recent randomized clinical trials for alopecia areata, atopic dermatitis, psoriasis, systemic lupus erythematosus (SLE), vitiligo, systemic sclerosis (SSc), and hidradenitis suppurativa (HS). By identifying disparities in representation, we aim to inform strategies that ensure equitable access to emerging therapies and contribute to broader efforts to eliminate health inequities in dermatology.

## MATERIALS AND METHODS

### Search Strategy

We conducted a systematic search of ClinicalTrials.gov and

PubMed for published results of clinical trials evaluating JAK inhibitors for alopecia areata, atopic dermatitis, hidradenitis suppurativa, psoriasis, systemic sclerosis, systemic lupus erythematosus, and vitiligo between 2000 and 2025. We included all peer-reviewed English-language completed trials of all phases that reported racial and ethnic demographic data for enrolled participants. Keywords included “jak inhibitors,” “atopic dermatitis,” “vitiligo,” “alopecia areata,” “systemic sclerosis,” “systemic lupus erythematosus,” and “hidradenitis suppurativa” and were applied to titles, abstracts, and full articles. Reviewers screened titles and abstracts prior to data extraction and excluded animal studies, duplicate studies from across different studies, and those unrelated to JAK inhibitors or the conditions being studied.

Included studies were studies that occurred within the designed search criteria and that addressed the conditions of interest. Each article’s title and abstract were initially screened to exclude non-dermatologic studies, non-JAK inhibitor studies, and those based on animal models. The full text of all remaining articles was then reviewed in detail. Exclusion criteria included clinical trials with incomplete results or results not posted were not included in this study. Duplicated reports of the same study across different sources were excluded, with only the most recent or comprehensive report retained.

### Race and Ethnicity Categorization

Race and ethnicity were categorized according to the standards of the ClinicalTrials.gov online database maintained by the National Library of Medicine. This included the following classifications: White, Black/African American, Asian, Native Hawaiian or Pacific Islander, American Indian, Multi-racial, and Others. Ethnicity was categorized using the classification of Hispanic or Non-Hispanic.

### Data Abstraction

Reviewers screened the studies and extracted data on the dermatologic condition studied, the JAK inhibitor tested, sample size, and racial and ethnic composition of enrolled participants, Fitzpatrick Skin Type (FST), age, and quality of life measure. Study data were collected and managed using tools in a spreadsheet. In addition to demographic variables, we extracted target dermatologic condition, total sample size, and sponsorship source (categorized as industry, university, or NIH). Multiple publications stemming from the same study or patient cohort were treated as independent entries for analysis. All data were obtained from public online databases; institutional review board approval was not required.

### Statistical Analysis

Data were analyzed via descriptive analysis of collective demographic variables, evaluating frequencies of each category. We then compared the racial and ethnic distribution

of participants in these trials to the estimated racial prevalence of each condition in the US population, using averaged prevalence data from reference epidemiologic studies. Statistical significance of study differences by race and ethnicity representation was determined by  $\chi^2$  tests or Fisher exact tests where appropriate. Pearson residuals were calculated in order to measure the direction of the difference assuming the collected data is treated as observed and the reference data as expected outcomes.

## RESULTS

A total of 399 unique studies eligible for analysis were identified. After screening abstracts, 192 were excluded due to focus on non-dermatologic conditions, as duplicates, animal studies, or covering diseases outside of our inclusion criteria. Two-hundred

seven (207) unique trials were ultimately reviewed (Figure 1). Trials included a total of 91,873 study participants across all studies. Age was collected in a majority of studies (80.68%) with a mean age of 34.1 amongst study participants. A majority of the studies were industry-sponsored (83.6%), while 16.9% were primarily institution or National Institute of Health (NIH)-funded studies.

### Reporting on Racial Data

A total of 207 clinical trials were included in our analysis, of which 57.49% reported racial data, resulting in 57,112 study participants analyzed for racial demographics. Among studies reporting race, representation was predominantly White (75.1%), followed by Asian (13.2%), Black (6.6%), American Indian/Alaska Native (0.48%), Native Hawaiian (0.11%), and Multiple races (0.43%)

**FIGURE 1.** PRISMA flow diagram for study inclusion.

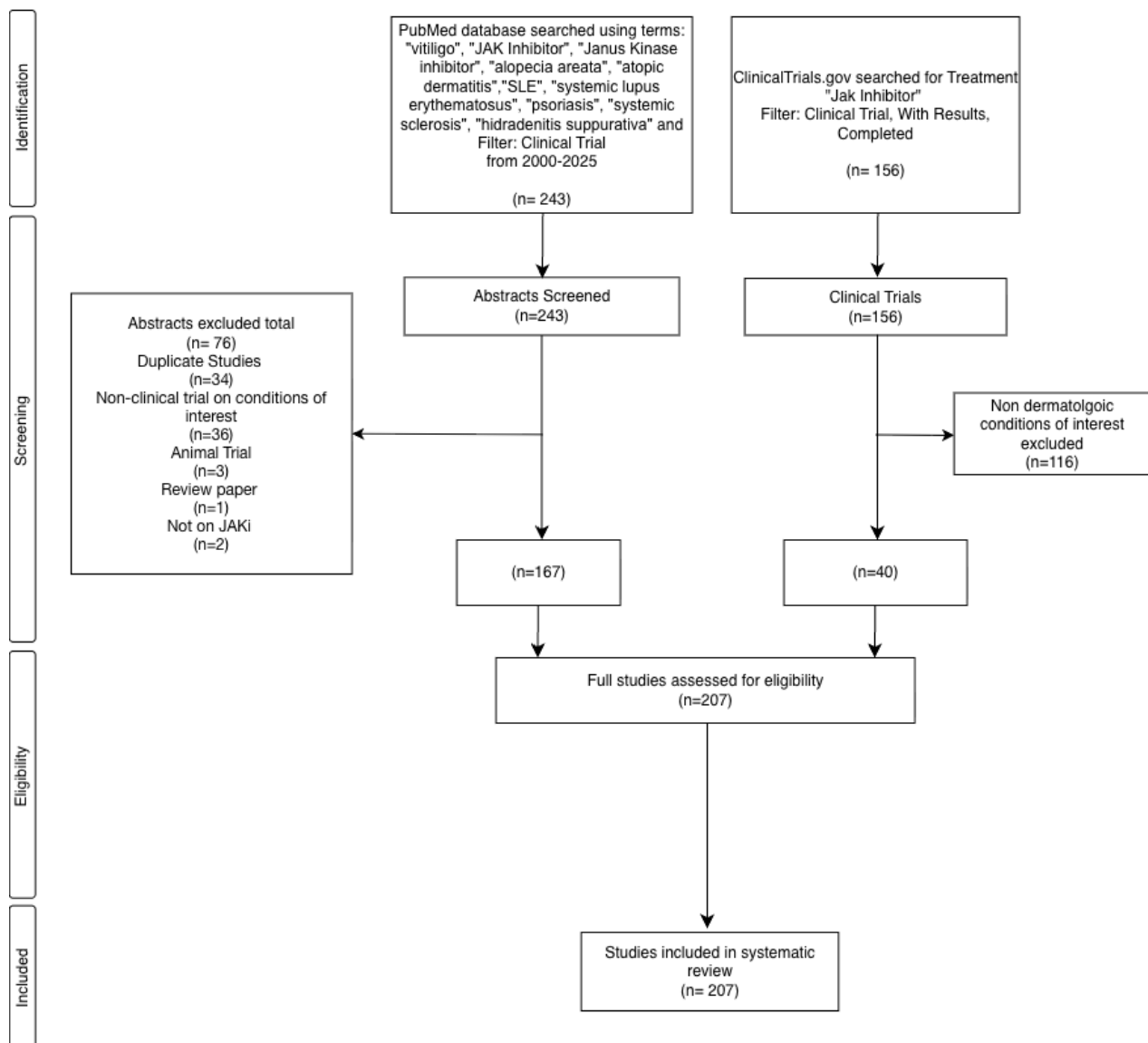


TABLE 1.

| Summary of Racial Representation in JAK Inhibitor Clinical Trials |                            |               |                                |                                       |                      |              |             |               |                   |                    |
|-------------------------------------------------------------------|----------------------------|---------------|--------------------------------|---------------------------------------|----------------------|--------------|-------------|---------------|-------------------|--------------------|
|                                                                   | Studies Reporting Race (%) | Reported Race |                                |                                       |                      |              |             |               |                   | Total Participants |
|                                                                   |                            | White n(%)    | Black or African American n(%) | American Indian or Alaska Native n(%) | Native Hawaiian n(%) | Asian n(%)   | Other n(%)  | Multiple n(%) | Not Reported n(%) |                    |
| Alopecia Areata                                                   | (71.43)                    | 4509 (67.71)  | 430 (6.46)                     | 4 (0.06)                              | 6 (0.09)             | 1494 (22.43) | 129 (1.94)  | 6 (0.09)      | 81 (1.22)         | 6659               |
| Psoriasis                                                         | (42.25)                    | 16993 (86.78) | 258 (1.32)                     | 9 (0.046)                             | 6 (0.031)            | 1389 (7.09)  | 809 (4.13)  | 18 (0.091)    | 0                 | 19582              |
| HS                                                                | (85.7)                     | 341 (65.08)   | 146 (27.86)                    | 4 (0.76)                              | 0 (0)                | 18 (3.44)    | 14 (2.67)   | 1 (0.19)      | 0 (0)             | 524                |
| Atopic Dermatitis                                                 | (56.16)                    | 17348 (69.29) | 2778 (11.1)                    | 54 (0.223)                            | 44 (0.18)            | 3567 (14.25) | 468 (1.88)  | 169 (0.68)    | 608 (2.43)        | 25036              |
| Systemic Sclerosis                                                | (50)                       | 14 (93.3)     | 1 (6.67)                       | 0 (0)                                 | 0 (0)                | 0 (0)        | 0 (0)       | 0 (0)         | 0 (0)             | 15                 |
| Systemic Lupus Erythematosus                                      | (78.57)                    | 2148 (65.61)  | 33 (1.01)                      | 197 (6.02)                            | 2 (0.061)            | 797 (24.34)  | 25 (0.76)   | 43 (1.31)     | 29 (0.89)         | 3274               |
| Vitiligo                                                          | (83.33)                    | 1563 (77.3)   | 103 (5.09)                     | 7 (0.35)                              | 4 (0.20)             | 255 (12.61)  | 43 (2.13)   | 11 (0.54)     | 36 (1.78)         | 2022               |
| All Studies                                                       | (57.49)                    | 42916 (75.14) | 3749 (6.56)                    | 275 (0.48)                            | 62 (0.11)            | 7520 (13.17) | 1488 (2.61) | 248 (0.43)    | 754 (1.32)        | 57112              |
| US Population <sup>57</sup>                                       | --                         | (75.3)        | (13.7)                         | (1.3)                                 | (0.3)                | (6.4)        | (19.5)§     | (3.1)         | --                | P-value = 0.000077 |

§Reported Hispanic/Latino in the US Census

(Table 1). Amongst each condition, non-White patients were particularly underrepresented. This was particularly pronounced amongst Black patients in clinical trials for psoriasis (1.3%), SLE (1.0%), and vitiligo (5.1%). However, there was a particularly high representation of Black patients for HS trials (27.9%). Specifically, for conditions with readily available prevalence data, representation in these trials significantly differed from the racial distribution of US patients with vitiligo ( $P=0.012$ ) and atopic dermatitis ( $P=0.00088$ ) (Table 2). White patients were overrepresented in vitiligo and AD (Pearson residual=1.06, 2.71), while Black patients were underrepresented (Pearson residual=-2.66, -2.14). However, this difference in representation was not significant for psoriasis, with White populations overrepresented insignificantly ( $P=0.054$ ) (Table 2).

Reporting on Ethnic Data

Limited granular data were available for ethnicity due to limitations in NIH reporting guidelines for clinical trials. Additionally, a small minority of studies collected ethnic data (19.80%), likewise with FST (2.42%), which limited further analysis. Of available ethnicity data collected, there were no differences between the US Hispanic population representation and representation across all of the clinical trials for JAK inhibitors ( $P=0.211$ ) (Tables 3 and 4). This held true when comparing clinical trial representation to disease prevalence for psoriasis, AD, and vitiligo in the United States ( $P=0.060$ , 0.072, 0.29).

TABLE 2.

| Race Representation in JAK inhibitor Clinical Trials Compared to Prevalence in the United States                         |               |                                |           |           |         |
|--------------------------------------------------------------------------------------------------------------------------|---------------|--------------------------------|-----------|-----------|---------|
|                                                                                                                          | Reported Race |                                |           |           | P-value |
|                                                                                                                          | White n(%)    | Black or African American n(%) | Other (%) | Total (%) |         |
| <b>Psoriasis</b><br>JAK inhibitor Clinical Trials<br>United States Prevalence <sup>58</sup><br>Pearson residuals         | 86.78         | 1.32                           | 11.39     | 99.49     | 0.054   |
|                                                                                                                          | 78            | 5.7                            | 16.3      | 100       |         |
|                                                                                                                          | 0.99          | -1.83                          | -1.22     | --        |         |
| <b>Atopic Dermatitis</b><br>JAK inhibitor Clinical Trials<br>United States Prevalence <sup>59</sup><br>Pearson residuals | 69.29         | 11.1                           | 19.61     | 100       | 0.00088 |
|                                                                                                                          | 50.11         | 20.8                           | 27.25     | 98.25     |         |
|                                                                                                                          | 2.71          | -2.14                          | -1.46     | --        |         |
| <b>Vitiligo</b><br>JAK inhibitor Clinical Trials<br>United States Prevalence <sup>60</sup><br>Pearson residuals          | 77.30         | 5.09                           | 17.61     | 100       | 0.012   |
|                                                                                                                          | 68.5          | 15.6                           | 14.5      | 98.6      |         |
|                                                                                                                          | 1.06          | -2.66                          | 0.82      | --        |         |

TABLE 3.  
Ethnicity Representation in JAK inhibitor Clinical Trials Compared to Prevalence in the United States

|                                                                                                                                 | Reported Ethnicity |                  |           | P-value |
|---------------------------------------------------------------------------------------------------------------------------------|--------------------|------------------|-----------|---------|
|                                                                                                                                 | Hispanic (%)       | Non-Hispanic (%) | Total (%) |         |
| <b>Psoriasis</b><br>JAK inhibitor Clinical Trials<br>United States Prevalence <sup>58</sup><br><i>Pearson residuals</i>         | 14.77              | 85.23            | 100       | 0.060   |
|                                                                                                                                 | 9.3                | 90.7             | 100       |         |
|                                                                                                                                 | 1.79               | -0.57            | --        |         |
| <b>Atopic Dermatitis</b><br>JAK inhibitor Clinical Trials<br>United States Prevalence <sup>59</sup><br><i>Pearson residuals</i> | 12.70              | 87.3             | 100       | 0.087   |
|                                                                                                                                 | 19.47              | 80.53            | 100       |         |
|                                                                                                                                 | -1.53              | 0.75             | --        |         |
| <b>Vitiligo</b><br>JAK inhibitor Clinical Trials<br>United States Prevalence <sup>60</sup><br><i>Pearson residuals</i>          | 19.08              | 80.92            | 100       | 0.29    |
|                                                                                                                                 | 15.3               | 84.7             | 100       |         |
|                                                                                                                                 | 0.96               | -0.41            | --        |         |

\* Individuals not reported were classified as Non-Hispanic

TABLE 4.  
Summary of Ethnicity

|                              | Reported Ethnicity              |               |                   |                   | Total Participants |
|------------------------------|---------------------------------|---------------|-------------------|-------------------|--------------------|
|                              | Studies Reporting Ethnicity (%) | Hispanic n(%) | Not Hispanic n(%) | Not Reported n(%) |                    |
| Alopecia Areata              | (25)                            | 331 (10.67)   | 2772 (89.33)      | 0 (0)             | 3103               |
| Psoriasis                    | (2.94)                          | 267 (14.78)   | 1540 (85.22)      | 0 (0)             | 1807               |
| HS                           | (28.57)                         | 15 (19.23)    | 63 (80.77)        | 0 (0)             | 78                 |
| Atopic Dermatitis            | (19.18)                         | 1292 (12.70)  | 8333 (81.93)      | 546 (5.37)        | 10171              |
| Systemic Sclerosis           | (50)                            | 0 (0)         | 15 (100)          | 0 (0)             | 15                 |
| Systemic Lupus Erythematosus | (50)                            | 254 (16.96)   | 522 (34.85)       | 722 (48.20)       | 1498               |
| Vitiligo                     | (66.67)                         | 314 (19.08)   | 1281 (77.83)      | 51 (3.10)         | 1646               |
| All Studies                  | (19.80)                         | 2473 (14.55)  | 14526 (85.45)     | --                | 16999              |
| US Population <sup>57</sup>  | --                              | 19.5          | 80.5              | --                | P-value = 0.211    |

Quality of Life (QoL) Measures

Additionally, a minority of studies (28.98%) reported on QoL metrics, which are essential tools for measuring disease burden and impact on patients. Among those reporting QoL, 56.67% were psoriasis studies, followed by atopic dermatitis (AD) studies (31.67%). The remaining studies that collected quality of life measures were for alopecia areata, vitiligo, and SLE. Quality of life measures reported included the Dermatology Life Quality Index (DLQI) for AD and psoriasis patients, Psoriasis Quality of Life (PQOL-12) for psoriasis patients, Family Dermatology Life Quality Index, and vitiQOL, specifically for vitiligo patients.

DISCUSSION

Our analysis shows a significant discrepancy in the inclusion and reporting of race and FST in JAK inhibitor clinical trials

for dermatologic conditions. Across all trials analyzed, 75.14% of participants were White, only 6.56% were Black or African American, and 13.17% were Asian, despite these groups comprising 75.3%, 13.7%, and 6.4% of the US population, respectively. These discrepancies are particularly troubling for inflammatory skin diseases such as atopic dermatitis, psoriasis, and vitiligo, which manifest differently and are associated with distinct complications in patients of color.<sup>24</sup> Failure to adequately represent these groups has critical implications for the generalizability, efficacy, and safety of emerging therapies.

Similar trends can be seen across dermatological conditions when comparing racial enrollment data by race to disease prevalence in the US In atopic dermatitis, although Black patients account for 20.89% of the disease burden in the US, they only

make up about 11.1% of clinical trial participants. In comparison, white patients, who account for 50.11% of disease prevalence, were overrepresented at 69.29% across all clinical trials. The trials for vitiligo also showed similar statistically significant trends of overrepresentation amongst White patients, with 77.3% represented in clinical trials compared to 68.5% in the actual population ( $P$ -value  $<0.05$ ). This suggests that current trial designs may not accurately represent the demographics of real patient populations.

There are few studies that explore the state of disease prevalence based on race. Our analysis was limited to three conditions for which this data was available. However, comparing all study participants to the demographic diversity of the United States population may reveal an underlying pattern of poor diverse representation of participants enrolled in JAK inhibitor clinical trials for dermatological conditions. When analyzing across all studies and indications, racial representation in trials differed significantly from the US population ( $P=0.021$ ).

These findings raise significant concerns. First, racial differences in pharmacodynamics may result from genetic diversity, cultural practices, and environmental exposures.<sup>25–27</sup> For example, genetic polymorphisms in drug-metabolizing enzymes, such as CYP450 variants, can influence how individuals process medications, altering efficacy or increasing the risk of adverse effects. Additionally, it has been well established that CYP450 plays a vital role in the pharmacokinetics and metabolism of oral forms of various JAK inhibitors.<sup>28,29</sup> Likewise, HLA-C variants may impact inflammatory disease processes and treatment response.<sup>30,31</sup> Cultural practices, including the use of traditional remedies, herbal treatments, or dietary modifications, may also interact with prescribed treatments.<sup>32</sup> Environmental exposures like UV radiation or pollution, which vary geographically and socioeconomically, can further modify skin physiology and drug response.<sup>33</sup> These multifactorial influences make it imperative to study diverse populations, as an undifferentiated approach to dermatologic treatment may perpetuate inequities in outcomes and safety. This could limit the applicability of findings, especially when evaluating side effects such as post-inflammatory hyperpigmentation (PIH).

There are several limitations to this study, particularly regarding inconsistent and incomplete demographic reporting across clinical trials. Many studies failed to include essential variables such as race, ethnicity, or Fitzpatrick skin type (FST), which significantly hampers the ability to perform meaningful subgroup analyses. Notably, only about 2% of trials reported FST; a particularly concerning omission given its relevance in dermatologic research for assessing skin tone and associated treatment outcomes.<sup>25</sup> It has often been seen in dermatology that disease phenotypes and treatment responses may differ by skin type.<sup>34–36</sup> Although patients with darker skin tones are

more likely to have PIH, its risk cannot be adequately assessed in clinical trials without racial representation and reporting variables like the Fitzpatrick skin type.<sup>37</sup>

In addition, current NIH reporting guidelines limit how ethnicity is reported, often treating it as a separate category from race rather than providing granular classifications such as Non-Hispanic White or Non-Hispanic Black. This approach, which differs from US Census reporting standards, may obscure true representation and lead to inaccurate conclusions about patient populations included in these trials. Due to the limited disaggregation of ethnicity data, it is particularly difficult to assess whether Hispanic/Latino individuals are adequately represented in JAK inhibitor trials. These gaps highlight the urgent need for standardized and comprehensive demographic reporting to identify and address underrepresentation and improve equity in dermatologic research. Considering recent modifications to financial resources by federally supported research institutions, it is essential that standardization becomes a shared responsibility, implemented by both governmental and industry sponsors.

Quality of life (QOL) assessments were another important but underreported component of these clinical trials. Although clinician assessments, such as the Physician Global Assessment, are objective measures that can be used, they do not capture patient perspectives on the overall effectiveness of their treatments.<sup>38</sup> Patient-reported outcomes (PROs) reflect the individual's lived experience with disease and treatment and are critical for evaluating satisfaction, adherence, and overall benefit.<sup>39–42</sup> Quality of life (QoL) measures must account for racial and ethnic differences because the lived experience of skin disease is not uniform across populations. Patients with skin of color often report greater psychosocial burden, yet this is frequently underrecognized in studies using generalized QoL instruments like the Dermatology Life Quality Index (DLQI), which was primarily validated in White European populations.<sup>43</sup> The tools may not fully reflect culturally specific concerns, social stigma, or how visible skin conditions uniquely affect individuals with darker skin tones. For instance, in vitiligo, depigmented patches are far more noticeable on darker skin, intensifying feelings of embarrassment, social isolation, and anxiety.<sup>44–46</sup> Studies have shown that Black and Hispanic patients report higher rates of psychological distress, including depression and low self-esteem, compared to White patients with the same clinical severity.<sup>16</sup> Similarly, in atopic dermatitis, skin of color patients are more prone to post-inflammatory hyperpigmentation, which can contribute to prolonged cosmetic and emotional distress that may not be captured by a conventional scoring system like the DLQI unless the patient links it to one of the general questions like embarrassment or social impact.<sup>47</sup> Although some studies included validated metrics such as The Dermatology Life Quality Index (DLQI) for psoriasis and atopic dermatitis, disease-

specific measures like the Psoriasis Quality of Life (PQoL-12), the Family Dermatology Life Quality Index, and vitiQoL for vitiligo were not consistently used.<sup>48-51</sup> Tools like the vitiQoL in vitiligo, which has been validated in multiple populations, offer targeted insight into these lived experiences and should be prioritized alongside standard metrics.<sup>52</sup> Without race-specific analysis, these nuances are missed, and clinicians lack the evidence needed to tailor treatment or address psychosocial burden. Consistent inclusion of race and validated, disease-specific QoL tools ensures clinical trial results are both representative and applicable to the diverse patients seen in practice.<sup>17,53</sup>

These observed disparities may be due to either poor concerted efforts in ensuring diversity in trial recruitment or myriad limitations and challenges in recruitment and retention, such as poor community relationships or distrust in clinical trials among minority populations, or socioeconomic barriers to transportation and time availability. Regardless of the cause, actionable solutions are urgently needed. The **VISIBLE** trial on diverse recruitment of psoriasis patients offers a successful model for diversifying enrollment in dermatologic research. Strategies included intentional site selection based on the diversity of patient populations and provider experience with skin of color; provision of cultural sensitivity training to enhance staff engagement and communication; and reduction of logistical barriers by offering transportation assistance and compensation for missed work.<sup>54</sup> The trial also addressed language and cultural accessibility by translating study materials and providing on-site interpreters. Notably, it allowed participants to self-identify race and ethnicity without forcing predefined categories, promoting inclusivity and respect for individual identity.<sup>54</sup> Incorporating similar strategies into trials investigating JAK inhibitors could meaningfully address current representation gaps and ensure that emerging therapies are truly inclusive and evidence-based. Utilizing this approach would provide space for more rigorous and scientifically sound research outcomes.

## CONCLUSION

We hope our findings serve as a call to action to increase racial diversity in patient recruitment, trial design, and reporting practices for dermatologic clinical trials. First, consistent and transparent demographic reporting must become a standard in investigator-initiated and industry-sponsored studies. Although the National Institute of Health has reporting guidelines, many industry-led studies fall outside those mandates.<sup>55,56</sup> Strengthening collaborations with community-based organizations can increase trial accessibility and foster inclusive participation. By producing more generalizable, equitable data, these interventions will benefit individual patients, the scientific community, and broader public health outcomes. In today's push for equitable healthcare, ensuring representative clinical trials is not merely a matter of inclusion but a prerequisite for clinical validity and fair health outcomes.

## DISCLOSURES

Dr Adotama serves consults or serves on an advisory board for Janssen, Regeneron, Pfizer, Procter and Gamble, and Bristol-Myers. The remaining authors have no conflicts of interest.

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AUTHOR CORRESPONDENCE

Prince Adotama MD

E-mail:..... Prince.Adotama@nyulangone.org

# Eruptive Lentiginosis Within Resolved Psoriasis Plaques: A Case Report and Systematic Review of the Literature

Andrew Kosharek MD,<sup>a</sup> Santanna Patterson MS,<sup>a</sup> Di Yan MD<sup>a</sup>

<sup>a</sup>Department of Dermatology, University of Wisconsin School of Medicine and Public Health, Madison, WI

## ABSTRACT

**Background:** Many patients with psoriasis suffer from post-inflammatory pigmentary alteration (PIPA), which remains an unmet treatment need. Eruptive lentiginosis (EL) is a rare form of PIPA where multiple dark brown macules arise within a resolving psoriatic plaque. We present a case of a 68-year-old male with a history of chronic plaque psoriasis and prothrombin deficiency, who developed extensive EL following ixekizumab treatment. In addition, this article will discuss the current literature on risk factors, clinical outcomes, and treatments for EL.

**Methods:** The systematic literature review, conducted in accordance with PRISMA guidelines, utilized three databases, PubMed, SCOPUS, and CINAHL Plus, using search terms “psoriasis” and “lentigines” or “lentiginosis”. A total of 26 articles were identified and included.

**Results:** EL was reported in a diverse patient population with various Fitzpatrick skin types and ages ranging from 5 to 74 years old. Additionally, EL has developed in a wide array of treatments, including PUVA, NB-UVB, cyclosporine, acitretin, methotrexate, topicals, and biologics, with TNF inhibitors being the most common.

**Discussion:** The mechanism of EL is likely multifaceted, with potential mediators, such as UV radiation and inflammatory cytokines (TNF- $\alpha$ , IL-17, and IL-23), which may stimulate melanocyte proliferation. Additionally, our patient’s history of prothrombin deficiency suggests possible interplay between the coagulation cascade and melanogenesis in EL development. Patients and providers alike should be aware of the clinical course of EL, which, unlike other forms of PIPA, tends to persist without treatment. Potential treatment options for EL include the Q-switched ruby laser, which can lead to partial improvement.

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## INTRODUCTION

Psoriasis is a chronic inflammatory skin condition, affecting approximately three percent of the United States population. While modern therapeutic options for psoriasis have greatly improved symptom management and disease outcomes, many patients suffer from post-inflammatory pigmentary alteration (PIPA) even after their psoriatic disease is controlled.

PIPA includes hypopigmentation and hyperpigmentation and tends to disproportionately affect skin of color patients who can have pigmentary changes that are more visible, socially stigmatizing, and persistent. PIPA can have a profoundly negative impact on psychosocial health and quality of life with some patients regarding PIPA as more distressing than their inflammatory skin condition.<sup>1</sup> One study also found that 80 percent of patients felt their PIPA was a neglected aspect of psoriasis treatment, and 73 percent of patients saw PIPA as an unmet treatment need.<sup>2</sup>

Eruptive lentiginosis (EL) is a rare form of PIPA in which multiple dark brown macules arise within resolving psoriatic plaques. We present a case of a patient with extensive plaque psoriasis who developed eruptive lentiginosis within spontaneously resolved plaques that became more extensive following treatment with ixekizumab. We also review the literature on risk factors, clinical outcomes, and treatments for EL.

### Case Report

A 68-year-old male with Fitzpatrick skin type II presented with a 25-year history of chronic plaque psoriasis with psoriatic arthritis. The patient was previously treated with topical betamethasone and a narrowband UVB home unit. He utilized UVB treatment consistently for 3 years, followed by intermittent use for around 15 years. The patient discontinued use of the narrowband UVB home unit 2 years ago due to a lack of response. He had no history of prior treatment with systemic therapy. His past medical history is significant for prothrombin deficiency, childhood measles and mumps infection, and

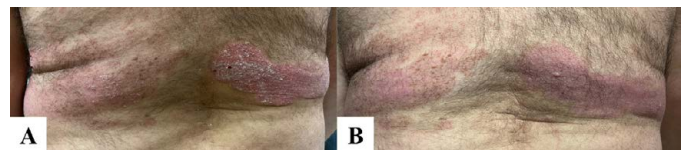
cardiovascular disease. On physical examination, the patient had scattered psoriatic plaques on the bilateral hands, back, chest, abdomen, scalp, and hair-bearing areas of the face, and nail involvement with oil spots and salmon patches. In addition, coalescing with the truncal plaques are well-demarcated, hyperpigmented erythematous patches, within which are numerous light brown macules without a true pigment network on dermoscopy. Total body surface area involved was around 20 percent. The light brown macules were consistent with lentigines that were limited to areas of psoriasis over the trunk. Ixekizumab treatment was initiated with a maintenance dose of 80 mg every four months, and a combination of moderate and high potency topical corticosteroids was applied to various body sites. Upon follow-up 6 weeks after initiation of ixekizumab, there was improvement of the patient's psoriatic plaques with interval development of more lentigines in areas of resolving plaques. Lentigines that were present prior to ixekizumab treatment were still present on the patient's trunk with no notable changes. The patient declined treatment for his lentigines and continued on ixekizumab with sustained control of his psoriatic disease.

## MATERIALS AND METHODS

This systematic review was conducted in accordance with PRISMA guidelines. A search of three databases, PubMed, SCOTUS, and CINAHL Plus, was done in March 2024 using the terms "psoriasis" and "lentigines" or "lentiginosis. From these three databases, 179 articles were identified. After duplicate

articles were removed, the remaining 119 articles were screened by authors SP and AK. Additional articles were identified through the bibliographies of included articles. Irrelevant articles, articles lacking primary data, and articles not available in English or full text were excluded. Articles included focused on the occurrence of eruptive lentiginosis (EL) in psoriasis patients and needed to contain patient demographic and treatment history.

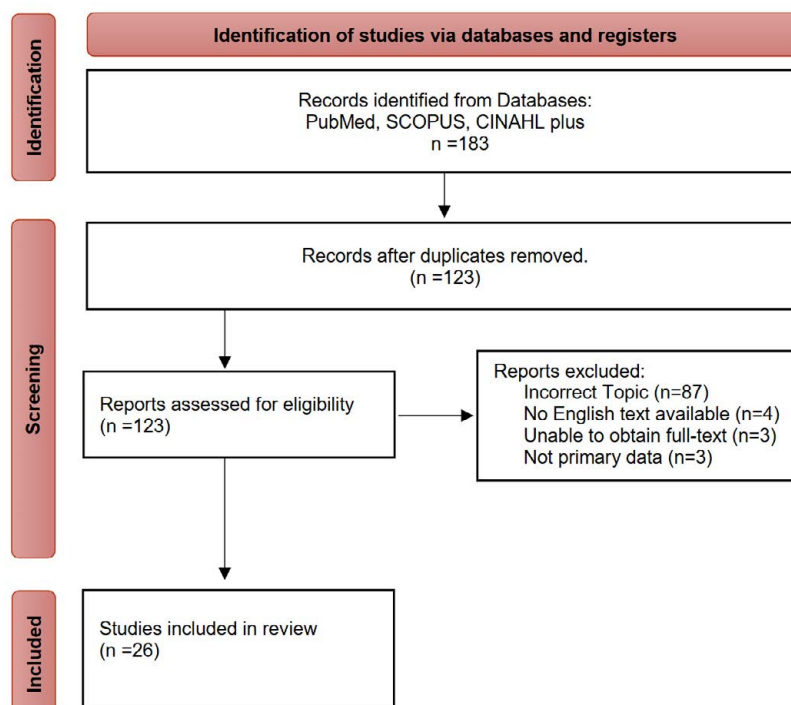
**FIGURE 1 A-B.** Eruptive lentigines within sites of psoriatic plaques on bilateral lower back (A) prior to ixekizumab treatment and (B) 6-weeks post-ixekizumab initiation.



**FIGURE 2 A-B.** Eruptive lentigines within sites of resolving psoriatic plaques on chest and abdomen (A) prior to ixekizumab treatment and (B) 6-weeks post-ixekizumab initiation.



**FIGURE 3.** PRISMA flow diagram of search for eruptive lentiginosis.



**TABLE 1.**

| Summary of Reported Cases of Eruptive Lentiginosis |                      |          |                       |                                                  |                                                                                         |                                                                                                                   |
|----------------------------------------------------|----------------------|----------|-----------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Reference                                          | Patient Demographics |          |                       | Clinical Presentation                            | Current Intervention                                                                    | Previous Intervention(s)                                                                                          |
|                                                    | Age (years)          | Sex      | Fitzpatrick Skin Type |                                                  |                                                                                         |                                                                                                                   |
| 4                                                  | 30                   | M        | III                   | Plaque psoriasis for >15-year duration           | Etanercept 50 mg twice weekly for 12 weeks, followed by 25 mg twice weekly for 6 months | PUVA<br>Cyclosporin<br>Acitretin<br>Methotrexate<br>Topical corticosteroids<br>Calcipotriol<br>Topical emollients |
|                                                    | 50                   | F        | II                    | Plaque psoriasis for 25-year duration<br>PASI 21 | Etanercept 50 mg twice weekly for 12 weeks, followed by 25 mg twice weekly for 20 weeks | Acitretin<br>Cyclosporin<br>UVB<br>Calcipotriol<br>Topical corticosteroids                                        |
| 7                                                  | 45                   | F        | NS                    | Plaques since adolescents                        | Adalimumab                                                                              | Topical therapies<br>Methotrexate<br>Cyclosporine                                                                 |
| 22                                                 | 65                   | M        | II                    | Plaque psoriasis for 30-year duration            | Calcipotriol for 3 months                                                               | Topical corticosteroids                                                                                           |
| 24                                                 | 12                   | F        | NS                    | Plaque psoriasis for 2-year duration             | Topical tacrolimus or pimecrolimus                                                      | Not disclosed                                                                                                     |
|                                                    | 37                   | M        | NS                    | Plaque psoriasis for 2.5-year duration           | Topical tacrolimus or pimecrolimus                                                      | Not disclosed                                                                                                     |
| 9                                                  | 43                   | M        | II                    | Plaque psoriasis since age 20, PASI 15 to 6      | Infliximab                                                                              | Topical corticosteroids<br>Retinoids<br>Calcipotriol<br>Cyclosporine<br>Systemic retinoids<br>Methotrexate        |
| 13                                                 | 40                   | M        | IV                    | Plaque psoriasis since age 15, PASI 19.6         | Ustekinumab 45mg every 12 weeks                                                         | Topical corticosteroids<br>Calcipotriol<br>Acitretin<br>Methotrexate                                              |
| 5                                                  | 14                   | M        | III                   | Plaque psoriasis since age 9, >50% BSA           | Etanercept 0 mg twice weekly for 3 months, followed by 50 mg weekly                     | Topical corticosteroids<br>NB-UVB                                                                                 |
|                                                    | 17                   | F        | II                    | Plaque psoriasis since age 12                    | Etanercept 50 mg twice weekly for 3 months, followed by 50 mg weekly                    | Topicals<br>NB-UVB                                                                                                |
|                                                    | 16                   | M        | III                   | Plaque psoriasis for 9-year duration, 40% BSA    | Etanercept 50 mg twice weekly for 3 months, followed by 50 mg weekly                    | Topical corticosteroids<br>Calcipotriol<br>Acitretin<br>Methotrexate                                              |
| 10                                                 | 55                   | F        | III                   | Plaque psoriasis for 12-year duration            | Infliximab                                                                              | Methotrexate<br>Adalimumab                                                                                        |
| 26                                                 | 55                   | M        | II                    | Chronic plaque psoriasis for 28-year duration    | Broad band UVB<br>Dithranol                                                             | NS                                                                                                                |
| 23                                                 | 74                   | F        | NS (I or II)          | Plaque psoriasis                                 | Coal tar<br>Dithranol<br>Topical corticosteroids                                        | NS                                                                                                                |
|                                                    | 56                   | M        | NS (I or II)          | Plaque psoriasis                                 | Coal tar<br>Dithranol<br>Topical corticosteroids                                        | NS                                                                                                                |
|                                                    | 41                   | F        | NS (I or II)          | Plaque psoriasis                                 | Coal tar<br>Dithranol<br>Topical corticosteroids<br>Calcipotriol                        | NS                                                                                                                |
|                                                    | 67                   | M        | NS (I or II)          | Plaque psoriasis                                 | Coal tar<br>Dithranol<br>Topical corticosteroids<br>UVB                                 | NS                                                                                                                |
| 25                                                 | 7                    | M        | NS                    | Plaque psoriasis                                 | Coal tar<br>Topical corticosteroids                                                     | NS                                                                                                                |
| 3                                                  | 53                   | F        | NS                    | Psoriasis                                        | Etanercept                                                                              | Topicals<br>Acitretin<br>Methotrexate                                                                             |
|                                                    | 60                   | M        | NS                    | Psoriasis                                        | Etanercept                                                                              | Unspecified systemic therapies                                                                                    |
| 19                                                 | NS                   | 3 F, 2 M | III to IV             | Plaque psoriasis                                 | Apremalast 30 mg twice a day for 5 years duration                                       | Topicals (n=5)<br>Acitretin (n=1)<br>Methotrexate (n=3)                                                           |

RESULTS

In total, 26 studies spanning from 1995 to 2023 were found (Figure 3). These studies showed that EL affects a diverse demographic of patients aged 5 to 74 with various Fitzpatrick skin types and diverse treatment histories (Table 1). Therapies prior to the onset of EL included PUVA, NB-UVB, cyclosporine, acitretin, methotrexate, and topical agents such as calcipotriol, tacrolimus, pimecrolimus, and topical corticosteroids (TCS). In addition, 3 patients had also failed adalimumab prior to developing EL on an alternative biologic.

The onset of EL was associated with a wide range of biologic therapies. The most commonly encountered biologics were TNF inhibitors including etanercept,<sup>3-5</sup> adalimumab,<sup>6-8</sup> and infliximab.<sup>9,10</sup> Amongst IL-17 inhibitors, secukinumab<sup>11</sup> and

ixekizumab,<sup>12</sup> including our current case, were reported in association with EL. Other patients developed EL during treatment with ustekinumab,<sup>13-15</sup> an inhibitor of the p40 subunit common to both IL-12 and IL-23. EL was also reported in association with IL-23 inhibitors like guselkumab,<sup>16</sup> risankizumab,<sup>17</sup> and tildrakizumab.<sup>18</sup>

EL has also been noted to arise in the setting of treatment with non-biologic systemic medications such as apremilast,<sup>19,20</sup> a PDE4 inhibitor that broadly modulates inflammatory pathways and methotrexate,<sup>21</sup> a dihydrofolate reductase inhibitor. Lastly, some patients developed EL during treatment with topical agents such as calcipotriol,<sup>22,23</sup> calcineurin inhibitors,<sup>24</sup> topical corticosteroids,<sup>23,25</sup> and coal tar derivatives.<sup>23,25,26</sup>

TABLE 1.  
Summary of Reported Cases of Eruptive Lentiginosis

| Reference | Patient Demographics |     |                       | Clinical Presentation                                             | Current Intervention                                                                                      | Previous Intervention(s)                              |
|-----------|----------------------|-----|-----------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
|           | Age (years)          | Sex | Fitzpatrick Skin Type |                                                                   |                                                                                                           |                                                       |
| 12        | 56                   | M   | III                   | Severe plaque psoriasis for 10-year duration, 62% BSA, PASI 38.9  | Ixekizumab 160 mg at week 0, 80 mg every 2 weeks for 3 months, followed by 80 mg every 4 weeks thereafter | Topical corticosteroids<br>Methotrexate               |
| 15        | 29                   | M   | III to IV             | Chronic plaque psoriasis for 6-year duration, 20% BSA             | Ustekinumab                                                                                               | None                                                  |
| 16        | 41                   | M   | IV                    | Plaque psoriasis for 15-year duration                             | Guselkumab                                                                                                | Topical corticosteroids                               |
| 21        | 40                   | M   | NS                    | Chronic plaque psoriasis for 4-year duration, PASI 15             | Methotrexate 15 mg weekly                                                                                 | Home-based remedies and alternative medicine          |
|           | 30                   | M   | IV                    | Chronic plaque psoriasis for 15-year duration, PASI 28            | Methotrexate 15 mg weekly                                                                                 | Alternative medicine<br>Topical corticosteroids       |
| 20        | 61                   | M   | II                    | Plaque psoriasis for 30-year duration, History of renal carcinoma | Apremilast                                                                                                | Phototherapy<br>Calcipotriol<br>Topical betamethasone |
| 6         | 45                   | F   | NS                    | Chronic plaque psoriasis since adolescence                        | Adalimumab                                                                                                | Topical therapies<br>Methotrexate<br>Cyclosporine     |
| 11        | 46                   | M   | NS                    | Severe chronic psoriasis vulgaris for 10-year duration, 90% BSA   | Secukinumab 300 mg for 4 months, followed by 300 mg every other month                                     | Topical emollients                                    |
| 18        | 50                   | M   | NS                    | Plaque psoriasis for 4-year duration                              | Tildrakizumab 100 mg every 12 weeks                                                                       | Topical corticosteroids<br>Methotrexate<br>Adalimumab |
| 14        | 48                   | M   | II                    | Plaque psoriasis since adolescence, PASI 25                       | Ustekinumab                                                                                               | Topical emollients<br>Methotrexate                    |
| 17        | 30                   | F   | NS                    | Severe chronic psoriasis vulgaris, 50% BSA, PASI 10               | Risankizumab 150 mg every 3 months for 24 months                                                          | Cyclosporin<br>Adalimumab                             |
| 8         | 55                   | M   | NS                    | Psoriasis vulgaris for 6-year duration, PASI 6.0                  | Adalimumab 80 mg, followed by 40 mg every other week                                                      | Topical corticosteroids                               |

Biopsies of affected sites showed elongation of rete ridges, pigmentation of epidermal keratinocytes, and a slightly increased number of epidermal melanocytes, findings similar to that seen in de novo lentigines.<sup>15,24</sup>

## DISCUSSION

A variety of mechanisms have been proposed for the pathogenesis of EL in patients undergoing treatment for psoriasis. Older studies from the 1980's initially linked the development of widespread lentigines to psoralen plus ultraviolet A (PUVA) radiation in so-called "PUVA lentigines", which were seen in 21 to 51% of PUVA cohorts.<sup>27-30</sup> In these studies, the risk of developing PUVA lentigines increased with more treatment sessions and higher doses of PUVA therapy. These studies were not included in our systematic review because PUVA lentigines are not always confined to the sites of psoriasis lesions, can demonstrate melanocyte atypia, and may not represent the same exact phenomenon as EL. Nonetheless, it is possible that EL and PUVA lentigines have shared UV-mediated pathways of pathogenesis. Although many patients, including our patient were not undergoing phototherapy at the time of EL onset, it is possible that UV radiation from natural sun exposure contributed to the development of some lesions.

However, UV radiation may not be the sole mediator of EL formation as some patients had no history of phototherapy treatment and developed EL in sun-protected areas such as the groin and intertriginous areas.<sup>24</sup> Other potential mediators of EL development include inflammatory cytokines, such as TNF- $\alpha$ , IL-17, and IL-23, which can cause epidermal acanthosis and simultaneously stimulate melanocyte proliferation while decreasing melanin production.<sup>5-12,14-17,20,31</sup> Thus, rapid reduction of psoriatic inflammation may lead to a post-inflammatory surge in hyperpigmentation from the increased melanocytes within psoriatic plaques.<sup>4,13,18,22</sup> Additionally, some psoriasis therapies have been implicated in promoting melanocytic activity and tyrosinase activation.<sup>19,21,24</sup>

Interestingly, our patient has a history of prothrombin deficiency, which leads to impaired fibrin clot formation and increased risk of bleeding. Recent studies suggest a possible connection between the coagulation cascade, specifically the fibrin-plasminogen system, and melanogenesis.<sup>32</sup> Tranexamic acid, which is commonly used to treat disorders of hyperpigmentation, inhibits plasminogen binding to keratinocytes and decreases the activity of melanocyte tyrosinase.<sup>33</sup> Tranexamic acid is also used in the setting of acute hemorrhage to inhibit plasminogen activation and degradation of fibrin clots. It is possible that variations in coagulation pathway genes could predispose individuals to an altered pigmentary response following inflammation and contribute to the development of EL.

Of note, EL is not exclusive to psoriasis and has been observed in other inflammatory conditions, patients undergoing

chemotherapy,<sup>34,35</sup> and even familial or idiopathic cases.<sup>36</sup> This wide range of associated conditions suggests that a complex interplay between genetic, inflammatory, and environmental factors may contribute to the etiology of EL.

The clinical course of EL often parallels that of post-inflammatory pigmentary alteration; however, unlike other forms of PIPA, which may resolve over time, eruptive lentigines tend to persist without active treatment.<sup>14,26</sup>

As EL is a rarer form of PIPA, there is limited data on treatment. Treatment with Q-switched ruby laser (QSRL) led to partial improvement of EL, but Q-switched frequency-doubled (KTP) Nd:YAG laser (QSFDNYL), which has been used successfully for solar lentigo, was not effective for the same patient.<sup>26</sup> Other treatment modalities such as pulsed dye laser (PDL), tretinoin, and topical cysteamine, which have been used for solar lentigo have not, to our knowledge been trialed in EL. PUVA lentigines have been successfully treated with cryotherapy and may be considered in patients with EL, although the benefits should be weighed against the risk of post-treatment dyspigmentation. While topical calcipotriol has been reported to improve PUVA lentigines, it was also associated with the development of EL in some patients.<sup>22,23</sup> Treatments for post-inflammatory hyperpigmentation, such as tranexamic acid, while not specifically investigated for use in EL, may be of benefit, especially given shared melanogenesis and coagulation pathways. For patients concerned about PIPA, counseling about the importance of sun protection during psoriasis treatment may help reduce UV-associated risk factors for EL.

## CONCLUSION

In conclusion, EL represents a complex dermatological condition with a potential etiology that spans genetic, inflammatory, and possibly pharmacological factors. Further research is needed to determine the precise mechanisms and optimize treatment strategies that consider the individual patient's genetic background.

## DISCLOSURES

The authors have no conflicts of interest to declare.

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AUTHOR CORRESPONDENCE

Di Yan MD

E-mail:..... dyan@dermatology.wisc.edu

# An Investigator-Developed Regimen for Treatment and Prevention of Post-Inflammatory Hyperpigmentation in Skin of Color

Kayla Zafar BA,<sup>a,b</sup> Margaret Kabakova BS,<sup>a,c</sup> Lucie Joerg BA,<sup>a,d</sup> Jared Jagdeo MD MS<sup>a,c</sup>

<sup>a</sup>Dermatology Service, Veterans Affairs New York Harbor Healthcare System – Brooklyn Campus, Brooklyn, NY

<sup>b</sup>St. George's University School of Medicine, Grenada, West Indies

<sup>c</sup>Department of Dermatology, State University of New York, Downstate Health Sciences University, Brooklyn, NY

<sup>d</sup>Albany Medical College, Albany, NY

## ABSTRACT

**Background:** There is an unmet demand for a post-inflammatory hyperpigmentation (PIH) treatment and prevention that is not only effective and accessible, but also safe to use in darker skin tones.

**Objective:** To evaluate the safety and efficacy of a comprehensive investigator-developed skincare regimen in reducing post-inflammatory hyperpigmentation (PIH) and improving patient-reported satisfaction in skin of color patients.

**Materials and Methods:** In this single-center, prospective, non-blinded, non-randomized 12-week study, ten participants with a diagnosis of PIH and identified as skin of color received two SkinCeuticals Pigment Balancing Peel treatments at baseline and week 6, Discoloration Defense Serum, Hydrating B5 Gel, LHA Cleanser Gel, and Daily Brightening ultraviolet (UV) Defense Sunscreen. Assessments were conducted at baseline, week 6, and week 12. The primary endpoint was the change in satisfaction with overall facial appearance post-treatment. Secondary endpoints included changes in the Dermatology Life and Quality Index (DLQI), FACE-Q social and psychosocial functioning, erythema and melanin index, and expectations and satisfaction with treatment.

**Results:** Participants reported significantly greater satisfaction with overall facial appearance at 12 weeks post-treatment compared to baseline ( $P<0.001$ ). Improvements were also observed in quality of life, with Dermatology Life Quality Index scores decreasing significantly ( $P<0.001$ ). Patients reported enhancements in skin texture and tone, social confidence, and psychological functioning. High levels of satisfaction with the treatment regimen and minimal adverse effects were noted across participants.

**Conclusion:** This investigator developed a comprehensive skincare regimen that combines a series of chemical peels with a daily at-home treatment regimen is a safe and effective approach for improving post-inflammatory hyperpigmentation, enhancing satisfaction with facial appearance, and promoting psychosocial well-being in individuals with skin of color.

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## INTRODUCTION

Post-inflammatory hyperpigmentation (PIH) is a common acquired condition resulting from an overproduction of melanin or abnormal deposition of melanin in the epidermis or dermis following inflammation.<sup>1</sup> PIH can appear following several types of inciting inflammatory factors, such as acne, atopic dermatitis, burns, wounds, insect bites, allergic reactions, or psoriasis.<sup>2</sup> PIH can be difficult to treat and impact patients' self-esteem.<sup>3</sup> This condition can improve spontaneously, but usually takes months to years to fade, creating a need for long-term treatment.<sup>1</sup> PIH is particularly prominent in the skin of color, greatly affecting quality of life and causing profound psychosocial distress.<sup>1,3,4</sup> One study found that 54% of patients felt embarrassment due to their hyperpigmentation with 22% experiencing a severe negative impact on their quality of life.<sup>5</sup> Another study found 51% of participants endorsing their PIH as more bothersome than the initial cause.<sup>6</sup>

The estimated prevalence of PIH among African Americans is reported to be as high as 9.99%.<sup>7</sup> PIH is one of the leading causes for cosmetic consultation, and accounts for the high demand for effective skin lightening therapies.<sup>8</sup> In 2022, the pigmentation disorders treatment market was estimated to be valued at 6.8 billion USD and is growing in demand.<sup>9</sup> The current treatments for PIH include topical lightening agents such as hydroquinone combined with a retinoid and steroid.<sup>1</sup> However, hydroquinone is associated with significant side effects such as skin lightening and permanent discoloration to the skin and ochronosis, limiting the ability to provide effective and well-tolerated treatment.<sup>10</sup> Steroids are also ineffective for long-term use due to the side effect of skin atrophy.<sup>10</sup> There is a lack of strong therapeutic options for treating PIH that are well tolerated, safe, effective, and accessible. In this study, we investigated the safety and efficacy of a comprehensive skincare regimen in the treatment of PIH among skin of color patients.

TABLE 1.

| Eligibility Criteria                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Inclusion Criteria                                                                                                                                                                                                                                                                                                                                                                  | Exclusion Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"><li>• Men and women ages 18+</li><li>• Clinical diagnosis of post-inflammatory hyperpigmentation</li><li>• Non-Caucasian</li><li>• Fitzpatrick skin types IV-VI</li><li>• Available and willing to comply with study instructions and attend all study visits</li><li>• Able and willing to provide written and verbal informed consent</li></ul> | <ul style="list-style-type: none"><li>• Subject has any skin pathology or condition that could interfere with the evaluation of the test products or requires the use of interfering topical or systemic therapy.</li><li>• Caucasian/ Non-Hispanic</li><li>• Subject has any condition which, in the investigator’s opinion, would make it unsafe for the subject to participate in this research study.</li><li>• Pregnant, lactating, or is planning to become pregnant during the study.</li><li>• Subject is currently enrolled in an investigational drug or device study.</li><li>• Subject has received an investigational drug or has been treated with an investigational device within 30 days prior to the initiation of treatment (baseline).</li><li>• Study participant has facial hair that could interfere with the study assessments in the opinion of the investigator.</li><li>• Study participant is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.</li><li>• Subject has known hypersensitivity or previous allergic reaction to any of the active or inactive components of the test articles.</li><li>• Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the trial.</li></ul> |

MATERIALS AND METHODS

Study Design

This single-center, prospective, non-blinded, non-randomized 12-week clinical study was conducted at the New York Harbor Veterans Affairs Brooklyn Campus between March and July 2025. The study protocol was approved by the New York Harbor Veterans Affairs Institutional Review Board, and all participants provided written informed consent prior to participating in this study.

Patients

Eligible participants were adults over the age of 18 years old with a clinical diagnosis of PIH and identified as skin of color and are Fitzpatrick skin types IV-VI. Detailed inclusion and exclusion criteria are listed in Table 1.

Study Products and Treatment Regimen

Participants received a comprehensive skincare regimen consisting of SkinCeuticals products (L’Oréal USA), including two in-office Pigment Balancing Peel treatments administered by a board-certified dermatologist, once at the initial study

visit and again at week 6. This chemical peel contains 40% unbuffered glycolic acid, 10% citric acid, 27% vitamin C, and 4% emblica. One week following the baseline peel, participants began a twice-daily at-home regimen for 12 weeks, including the products detailed in Table 2.

Efficacy Assessments

To evaluate the efficacy of the comprehensive skincare regimen, assessments were performed at baseline, week 6, and week 12. The primary outcome was the change in patient satisfaction with facial appearance from baseline to week 12, measured using the FACE-Q Satisfaction with Facial Appearance Overall Scale. Raw scores were converted to a 0–100 scale using the Rasch transformation, with higher scores indicating greater satisfaction. Secondary outcome measures included changes in quality of life as assessed by the Dermatology Life Quality Index (DLQI), which ranges from 0 to 30, with lower scores indicating better quality of life. Additional FACE-Q Aesthetic Scales were used to evaluate patient-reported satisfaction with treatment, psychological and social functioning, and overall outcome satisfaction.

TABLE 2.

| Key Ingredients of the SkinCeuticals Products Used in the Treatment Regimen |                                                                                        |
|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Product                                                                     | Key Ingredients                                                                        |
| Discoloration Defense Serum                                                 | Tranexamic acid, niacinamide, kojic acid, hydroxyethylpi-perazine ethane sulfonic acid |
| LHA Cleansing Gel                                                           | Lipo-hydroxy acid, glycolic acid, salicylic acid, glycerin, sorbitol                   |
| Hydrating B5 Gel                                                            | Hyaluronic acid, panthenol (provitamin B5)                                             |
| Daily Brightening UV Defense Sunscreen SPF 30                               | Broad-spectrum UV filters, tranexamic acid, niacinamide, phenylethyl resorcinol        |

**FIGURE 1.** Clinical improvement in PIH over 12 weeks of treatment. Standardized photographs of a participant at baseline (left), week 6 (middle), and week 12 (right) demonstrate progressive reduction in hyperpigmented lesions and improved skin tone uniformity.



At each study visit, skin measurements were performed using the Mexameter® (Courage + Khazaka, Cologne, Germany), a narrow-band reflectance spectrophotometer. Values for melanin and erythema index were recorded at predetermined facial regions where the patient had the most PIH. Three readings per site were averaged for accuracy. These measurements provided quantitative data on pigmentary changes and skin tone evenness throughout the treatment period. The Mexameter outputs unitless values: melanin index values typically range from 0 to 1,000+, with higher scores indicating increased pigmentation, while erythema index values range from 0 to 999, reflecting the degree of skin redness or inflammation. Standardized digital photography using theTwinFlash RL Clinical Camera (CanfieldSci, Parsippany, NJ) was captured at each visit. Consistent lighting, camera settings, and patient positioning were maintained to ensure comparability over time (Figure 1).

Statistical Analysis

All statistical analyses were conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA). Descriptive statistics, including means and standard deviations (SD), were calculated for all continuous variables. To evaluate treatment efficacy, paired t-tests were performed to compare values between time points (baseline vs. week 6, and week 6 vs. week 12) for the following outcomes: FACE-Q Satisfaction with Facial

Appearance scores, DLQI scores, and Mexameter® indices (melanin and erythema index). A two-tailed *P*-value < 0.05 was considered statistically significant. The raw scores of the primary outcome measure (FACE-Q Satisfaction with Facial Appearance Scale) were converted into a standardized 0–100 scale using the Rasch transformation method before analysis. Only participants who completed both baseline and follow-up assessments were included in the final analysis.

Adverse Events

Participants were closely monitored for the occurrence of adverse events (AEs) throughout the study period. They were instructed to record any treatment-related symptoms or concerns in a study diary and to promptly report any emergent issues to the research team.

RESULTS

Participants

Ten participants were enrolled and received the study treatment regimen. The majority were female (90%), and most identified as Black or African American (80%), with the remaining identifying as Hispanic or Latino (20%). The mean age was 47.1 years (range:

TABLE 3.

| Baseline Demographics of Participants |                   |
|---------------------------------------|-------------------|
| Characteristic                        | Total<br>(n = 10) |
| Age in years, mean ± SD               | 47.1 ± 13.23      |
| Sex, n (%)                            |                   |
| Female                                | 9 (90%)           |
| Male                                  | 1 (10%)           |
| Race and ethnicity, n (%)             |                   |
| Black or African American             | 8 (80%)           |
| Hispanic or Latino                    | 2 (20%)           |
| Fitzpatrick Skin Types, n (%)         |                   |
| Type IV                               | 2 (20%)           |
| Type V                                | 5 (50%)           |
| Type VI                               | 3 (30%)           |

TABLE 4.

| Patient Testimonials on Efficacy and Tolerability of the Skinceuticals Chemical Peels and Product Regimen |                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Patient Number                                                                                            | Patient Reviews                                                                                                                       |
| 1                                                                                                         | I love the overall end result my face is even tone and smooth.                                                                        |
| 2                                                                                                         | My face is glowing.                                                                                                                   |
| 3                                                                                                         | No comment.                                                                                                                           |
| 4                                                                                                         | No side effects. I enjoyed using the products.                                                                                        |
| 5                                                                                                         | Products were good. Didn't like the after effects of the peel.                                                                        |
| 6                                                                                                         | I love my outcome! When starting the regimen my skin was very dry and had to adjust to the moisturizer but my skin did within a week. |
| 7                                                                                                         | Overall good experience, products were very hydrating especially discoloration defense serum and sunscreen.                           |
| 8                                                                                                         | I love the outcome. I feel my face is glowing.                                                                                        |
| 9                                                                                                         | I definitely noticed a difference in the dark spots lightening or appearing lighter instead of darker.                                |
| 10                                                                                                        | No comment.                                                                                                                           |

30 to 70 years). Fitzpatrick skin types included Type IV (20%), Type V (50%), and Type VI (30%) (Table 3). All participants completed the study per protocol, with no participants lost to follow-up.

Safety and Tolerability

No severe AEs were reported during the study. Mild, treatment-related AEs were observed in 3 participants (30%) following administration of the Pigment Balancing Peel. Reported symptoms included transient redness, peeling, and burning. All events resolved spontaneously without the need for medical intervention and resulted in no long-term effects. No adverse events were reported with the use of the at-home products, including the Discoloration Defense Serum, Hydrating B5 Gel, LHA Cleansing Gel, or Daily Brightening UV Defense Sunscreen.

Efficacy

Patient Reported Outcomes

At the final study visit, all 10 participants completed a patient-reported outcomes (PRO) questionnaire assessing their experience with the treatment regimen. On a 0–4 scale, where 4 indicated “very noticeable improvement” and 0 indicated “no

improvement,” participants reported a high level of improvement in PIH (mean: 3.5 ± 0.71, 87.5%), overall facial appearance (mean: 3.4 ± 0.52, 85%), and the way their skin feels (mean: 3.4 ± 0.52, 85%). Satisfaction with the regimen was similarly high, with a mean overall satisfaction score of 3.5 ± 0.53, or 87.5%. When asked about their likelihood of recommending the treatment to others, the mean score was 3.4 ± 0.70 (85%). The skincare regimen was rated as very easy to use, with a mean difficulty score of 0.2 ± 0.42, where 0 indicated “very easy.” Reported side effects were minimal, with a mean score of 0.9 ± 1.29 (22.5%), indicating that most participants experienced few or no adverse symptoms. Table 4 summarizes patient testimonials regarding their overall experience with the investigator-designed chemical peels and PIH regimen.

Primary Outcome

*Satisfaction with Overall Facial Appearance:* At 12 weeks post-treatment, participants reported significantly greater satisfaction with their overall facial appearance compared to baseline. The mean satisfaction score increased from 41.8 ± 17.4 at baseline to 79.2 ± 16.1 post-treatment, reflecting an average 89.5%

TABLE 5.

| Erythema Index Measurementsa at Baseline, Week 6, and Week 12, Assessed Using the Mexameter® |                   |                 |                  |
|----------------------------------------------------------------------------------------------|-------------------|-----------------|------------------|
| Mexameter Erythema Measurement 1                                                             |                   |                 |                  |
| Participant                                                                                  | Erythema Baseline | Erythema Week 6 | Erythema Week 12 |
| 1                                                                                            | 471.0             | 464.3           | 464.4            |
| 2                                                                                            | 463.0             | 454.3           | 476.0            |
| 3                                                                                            | 386.0             | 393.0           | 420.0            |
| 4                                                                                            | 396.0             | 413.0           | 420.0            |
| 5                                                                                            | 454.0             | 463.0           | 461.0            |
| 6                                                                                            | 451.0             | 441.0           | 430.6            |
| 7                                                                                            | 423.0             | 445.3           | 453.6            |
| 8                                                                                            | 412.0             | 441.6           | 445.0            |
| 9                                                                                            | 461.0             | 459.3           | 470.6            |
| 10                                                                                           | 436.6             | 446.3           | 448.0            |
| Mexameter Erythema Measurement 2                                                             |                   |                 |                  |
| Participant                                                                                  | Erythema Baseline | Erythema Week 6 | Erythema Week 12 |
| 1                                                                                            | 460.3             | 462.3           | 468.3            |
| 2                                                                                            | 461.6             | 462.6           | 461.3            |
| 3                                                                                            | 421.6             | 416.3           | 430.0            |
| 4                                                                                            | 379.3             | 387.6           | 411.0            |
| 5                                                                                            | 435.6             | 456.0           | 452.0            |
| 6                                                                                            | 445.6             | 433.0           | 433.0            |
| 7                                                                                            | 420.6             | 424.0           | 438.0            |
| 8                                                                                            | 369.3             | 431.6           | 437.6            |
| 9                                                                                            | 456.6             | 463.3           | 445.6            |
| 10                                                                                           | 472.3             | 450.3           | 479.6            |

TABLE 6.

| Melanin Index Measurements at Baseline, Week 6, and Week 12, Assessed Using the Mexameter® |                  |                |                 |
|--------------------------------------------------------------------------------------------|------------------|----------------|-----------------|
| Mexameter Melanin Measurement 1                                                            |                  |                |                 |
| Participant                                                                                | Melanin Baseline | Melanin Week 6 | Melanin Week 12 |
| 1                                                                                          | 736.0            | 711.0          | 679.6           |
| 2                                                                                          | 830.0            | 846.0          | 822.0           |
| 3                                                                                          | 908.3            | 904.0          | 877.0           |
| 4                                                                                          | 898.0            | 873.0          | 865.0           |
| 5                                                                                          | 847.3            | 830.0          | 793.6           |
| 6                                                                                          | 627.0            | 623.3          | 599.0           |
| 7                                                                                          | 883.0            | 852.3          | 842.0           |
| 8                                                                                          | 895.0            | 862.3          | 838.0           |
| 9                                                                                          | 744.0            | 749.3          | 687.6           |
| 10                                                                                         | 870.3            | 841.6          | 839.3           |
| Mexameter Melanin Measurement 2                                                            |                  |                |                 |
| Participant                                                                                | Melanin Baseline | Melanin Week 6 | Melanin Week 12 |
| 1                                                                                          | 711.3            | 703.3          | 683.3           |
| 2                                                                                          | 804.3            | 798.6          | 757.3           |
| 3                                                                                          | 881.0            | 889.0          | 877.0           |
| 4                                                                                          | 907.0            | 900.7          | 882.3           |
| 5                                                                                          | 858.6            | 826.0          | 789.6           |
| 6                                                                                          | 608.3            | 603.0          | 599.0           |
| 7                                                                                          | 878.3            | 877.0          | 866.3           |
| 8                                                                                          | 906.6            | 873.0          | 855.0           |
| 9                                                                                          | 744.0            | 776.3          | 730.6           |
| 10                                                                                         | 836.6            | 820.3          | 815.6           |

improvement in satisfaction scores ( $P<0.001$ ). Refer to Figure 1 for clinical photographs highlighting the improvements in PIH observed.

Secondary Outcomes

**Erythema and Melanin Index:** Mexameter® measurements were used to quantify erythema and melanin levels at two facial sites affected by PIH. Data were collected at baseline, week 6, and week 12. A progressive decrease in melanin index was observed across most participants, indicating improvement in hyperpigmentation. Erythema index remained stable or slightly decreased over the course of treatment. Full individual values are presented in Tables 5 and 6.

**Dermatology Life Quality Index:** Significant improvements in quality of life were observed following treatment, as measured by the DLQI. The mean DLQI score decreased from  $6.5 \pm 6.6$  at baseline to  $0.7 \pm 1.3$  post-treatment, indicating a substantial reduction in the impact of skin disease on daily functioning ( $P<0.01$ ). Notably, 70% of participants reported a final DLQI

score of 0, reflecting no negative impact of their skin condition on quality of life after completing the regimen.

**Patient Expectations:** Patient expectations regarding the impact of treatment were evaluated at baseline using the FACE-Q Expectations Scale. The mean expectation score was  $84.8 \pm 20.1$  out of 100, indicating that participants generally anticipated a substantial positive effect from the treatment regimen. Notably, 60% of participants reported a perfect score of 100.

**Patient Satisfaction with Outcome:** Patient satisfaction with treatment outcome was assessed using the FACE-Q Outcome Satisfaction Scale. The average satisfaction score was  $82.5 \pm 17.9$  out of 100. High satisfaction was observed across participants, with 90% of patients reporting scores above 68, and 50% scoring 87 or higher.

**Psychosocial Functioning:** Participants completed the FACE-Q Psychological Function Scale at baseline and week 12. At baseline, the mean psychological function score was 64.6

(SD = 19.1), which increased to 94.6 (SD = 15.1) at week 12. This reflects a significant improvement of 46.4% in psychological well-being following treatment. Notably, 80% of participants achieved the maximum score of 100 at week 12, compared to only 20% at baseline.

**Social Functioning:** Participants completed the FACE-Q Social Function Scale at baseline and week 12. The mean baseline score was 66.3 (SD ± 23.58), which increased to a mean of 77.9 (SD ± 15.24) at week 12. This represents a 17.5% increase in social functioning scores post-treatment. Notably, 90% of participants either maintained or improved their social functioning scores, with 60% of participants scoring ≥ 90 on the final assessment.

## DISCUSSION

This prospective, single-center investigator-developed clinical trial found that combining the SkinCeuticals Pigment Balancing Peel with a targeted skincare regimen significantly improved PIH, patient-reported satisfaction, and quality of life in patients with skin of color. The primary outcome of this study was improvement in patient satisfaction with facial appearance, assessed by the FACE-Q Satisfaction with Facial Appearance Overall Scale. At week 12, participants reported a significant 89.5% increase in satisfaction with facial appearance, with mean scores increasing from 41.8 ± 17.4 at baseline to 79.2 ± 16.1 post-treatment ( $P < 0.001$ ). This significant improvement underscores the regimen's ability to enhance patients' perception of their skin, which is a key concern among individuals with PIH, especially in skin of color populations.

This aligns with findings from previous studies that have highlighted the psychosocial burden of PIH and the limitations of traditional treatments. While hydroquinone-based therapies may be effective, they have been associated with AEs such as exogenous ochronosis and irritant dermatitis, particularly with prolonged use.<sup>11</sup> In contrast, studies exploring alternative depigmenting agents such as tranexamic acid, niacinamide, and chemical peels (eg, glycolic acid) have demonstrated moderate efficacy with improved safety profiles.<sup>12,13</sup> However, few trials have combined these agents into a comprehensive regimen evaluated prospectively in skin of color patients. Our results expand upon this emerging evidence, showing that a multi-agent, hydroquinone-free treatment can offer significant improvement in both objective and subjective outcomes.

In addition to the primary outcome, multiple patient-reported outcomes improved significantly. Quality of life, as assessed by the DLQI, decreased from 6.5 ± 6.6 at baseline to 0.7 ± 1.3 at week 12 ( $P = 0.018$ ), indicating a marked reduction in the burden of PIH on daily functioning. The FACE-Q Psychological Function scale increased from 64.6 ± 19.1 to 94.6 ± 15.1 ( $P = 0.0008$ ), reflecting improved self-confidence and overall mental well-being. Similarly, FACE-Q Social Function scores

increased from 66.3 ± 23.6 to 77.9 ± 15.2 ( $P = 0.048$ ), suggesting enhanced confidence in social interactions. These PRO results are particularly meaningful given that previous studies on PIH have often focused on clinician-assessed outcomes rather than patient perspectives.<sup>14</sup> The use of patient-reported outcome measures such as the FACE-Q allows for a more comprehensive evaluation of treatment effectiveness, highlighting the patient experience.<sup>15</sup> Patients also reported high levels of treatment satisfaction, with a mean FACE-Q Outcome Satisfaction score of 82.5 ± 17.9. Additionally, 90% of participants felt their skin had improved, and 85% found the regimen easy to use, an important factor in treatment adherence. These findings reflect the growing demand for non-invasive, accessible solutions to pigmentary disorders that are safe and tolerable.

Despite these encouraging findings, our study has several limitations, including a small sample size of 10 participants, a lack of randomization, and the absence of a control group. These factors limit generalizability and introduce potential sources of bias. Additionally, the study was conducted during the late spring and summer months, when increased sun exposure may have influenced pigmentation outcomes despite the use of sunscreen, potentially confounding results. Larger, randomized controlled trials with longer follow-up periods are needed to confirm these results and determine the durability of treatment effects. This study contributes valuable evidence supporting a safe and efficacious treatment strategy for PIH in skin of color patients. The regimen significantly improved patient-reported satisfaction, psychological well-being, and quality of life over 12 weeks. These findings offer a foundation for further research into comprehensive, patient-centered therapies for pigmentary disorders.

## CONCLUSION

This prospective clinical trial found that an investigator-designed skincare regimen combining a chemical peel with daily at-home products significantly improved PIH and patient satisfaction in patients with skin of color. Patients reported greater satisfaction with facial appearance, glowing skin, improved quality of life, and reduced melanin index levels by spectrophotometer assessment. The regimen was well tolerated with minimal adverse effects. While the small sample size and lack of a control group are limitations, these findings support the potential of safe, accessible treatments for PIH in skin of color populations.

## DISCLOSURES

Kayla Zafar BA, Margaret Kabakova BS, and Lucie Joerg BA do not have any relevant conflicts of interest. Jared Jagdeo MD MS is the investigator for this investigator-initiated study. The New York Harbor VA Brooklyn Campus was the recipient of the grant funding.

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## AUTHOR CORRESPONDENCE

Jared Jagdeo MD MS

E-mail:..... jrjagdeo@gmail.com



10<sup>th</sup> ANNIVERSARY

## BEHIND THE BOTTLE PART DEUX: A SCIENTIFIC, SOCRATIC SQUAWK ON SENSITIVE AND SUSCEPTIBLE SKIN

Dr. Adam Friedman | Dr. Peter Lio

The JDD Podcast returns with Part 2 of “Behind the Bottle”, hosted by Dr. Adam Friedman, recorded live in front of attendees at ODAC 2026. Building on the wildly popular (so says Dr. Friedman’s mom) first installment with Dr. Peter Lio, this session once again pulls back the curtain on how clinicians can thoughtfully navigate the ever-expanding OTC universe, this time focusing on two increasingly common yet frequently misunderstood conditions: sensitive skin syndrome and dermatoporosis. These titans of too much talking share a dynamic, evidence-driven conversation that dissects the biology, clinical presentation, and real-world management challenges of sensitive skin syndrome, a state of cutaneous hyperreactivity marked by stinging, burning, and barrier dysfunction. The discussion will then shift to the misnomer dermatoporosis, the “osteoporosis of the skin,” highlighting its profound implications for an aging population, including fragility, tearing, and impaired wound healing. In classic JDD fashion for this milestone 100th episode, the podcast blends preclinical and clinical data, practical pearls, and Dr. Friedman’s signature wit to help clinicians make smarter, more confident product recommendations and care decisions. With the added energy and heckling of a live ODAC audience, this episode delivers a timely, high impact exploration of two conditions at the forefront of dermatologic practice.



HOST

Dr. Adam Friedman, MD, FAAD



GUEST

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# Beyond Efficacy: 0.6% Selenium Disulfide Shampoo Matches 2% Ketoconazole for Seborrheic Dermatitis With Superior Cosmesis

Patricia K. Farris MD,<sup>a</sup> Victoria Barbosa MD,<sup>b</sup> Elizabeth Bahar Houshmand MD,<sup>c</sup> Natalia Kovyalkina MD<sup>d</sup>

<sup>a</sup>Tulane University School of Medicine, New Orleans, LA

<sup>b</sup>University of Chicago Medical Center, Chicago, IL

<sup>c</sup>Houshmand Dermatology and Wellness, Dallas, TX

<sup>d</sup>Vichy Laboratoires, Paris, France

## ABSTRACT

**Background:** Although most dandruff shampoos are effective, many leave hair dry and unmanageable, potentially impacting patient compliance and treatment outcomes.

**Objective:** This study compared the efficacy, tolerability, and cosmetic benefits of 0.6% micronized selenium disulfide shampoo (SeS2) to 2% ketoconazole shampoo.

**Methods:** Eighty-seven male and female subjects with moderate to severe dandruff participated in a single-center, 6-week, randomized, double-blind study comparing the benefits and attributes of the shampoos.

**Results:** After 6 weeks of use, Total Scale Score (TSS) decreased by 69.5% in the ketoconazole group, and 77.9% in the SeS2 group, and Symptomatic Scale of Seborrheic Dermatitis (SSSD) decreased by 68.0% in the ketoconazole group and 74.5% in the SeS2 group (all  $P<0.001$ ). Pruritus severity score decreased by 76.2% and 75.9% in the ketoconazole and SeS2 groups, respectively, and global efficacy and satisfaction, as assessed by blinded dermatologic evaluation, showed significant improvement with both products (all  $P<0.001$ ). There was no significant difference between the two groups for these outcomes at any time point. Tolerability was excellent for both products. In terms of cosmesis, subjects across diverse curl types favored the SeS2 shampoo with significantly more agreeing that the SeS2 shampoo leaves hair soft, supple, glossy, natural appearing, and was suitable for their hair type when compared to ketoconazole ( $P<0.001$ ).

**Conclusion:** This micronized 0.6% SeS2 shampoo is as effective as 2% ketoconazole shampoo for treating moderate to severe scalp seborrheic dermatitis and provides superior cosmetic benefits across diverse curl types.

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## INTRODUCTION

Seborrheic dermatitis (SD) is a chronic, relapsing inflammatory condition. SD affects areas that are rich in sebaceous glands, most commonly the scalp (SSD).<sup>1</sup> In adults, SD occurs in approximately 1-3% of the general population, affecting men more often than women.<sup>2</sup> There is a spectrum of disease in SD that ranges from mild to severe.<sup>3</sup> Mild cases are sometimes referred to as dandruff or pityriasis sicca. This form of SD is characterized by dry flaking, often likened to snowflakes, which is noticeable on the scalp, hair shafts, and clothing. In more severe cases of SD, the inflammation may be more clinically evident with thick, greasy, yellowish flakes adherent to an erythematous scalp. The face is the second most affected area with similar appearing patches located symmetrically on the central face, nasolabial folds, alar creases, and eyebrows. SD can also affect the ear

canals, post-auricular area, neck creases, central chest, axillae, and inguinal folds. In melanin-rich skin, pink or hypopigmented annular coalescing ring-like scaling lesions, referred to as Petaloid SD, may be seen in and along the hairline and on the central face.<sup>4</sup> The primary symptom associated with all forms of SD is intense itching, although some patients note burning, stinging, and/or cosmetic product intolerance.<sup>5</sup> The burden of SD is significant, with sufferers experiencing not only physical signs and symptoms, but the embarrassment associated with unsightly visible flaking that can affect self-esteem.

The pathogenesis of SD is complex, and our understanding is still evolving. There appears to be an interplay between microbial colonization, altered lipid composition, and epidermal barrier dysfunction. In SD, there is an increased abundance of *Malassezia spp.* on the scalp that is related to disease

appearance and severity.<sup>6</sup> *Malassezia* are lipophilic commensal yeast that thrive in sebum-rich skin.<sup>7</sup> They secrete lipases that hydrolyze sebum triglycerides into saturated and unsaturated free fatty acids.<sup>8</sup> The saturated fatty acids serve as a nutrient source for *Malassezia*, while the unsaturated fatty acids, such as oleic acid and arachidonic acid, accumulate on the skin surface.<sup>9</sup> These unsaturated fatty acids are pro-inflammatory and impair barrier function. In addition, *Malassezia restricta* has been shown to oxidize squalene to squalene peroxides that increase oxidative stress, trigger inflammation, and alter epidermal proteins.<sup>10</sup> These altered proteins impair barrier function and cause flaking. Scalp affected by SD also shows an alteration in intercellular barrier lipids, including a change in the composition of ceramides that correlates with barrier dysfunction.<sup>11</sup> Environmental and genetic factors can be linked to SD.<sup>12</sup> Diet, physical and emotional stress, hormones, alcohol consumption, and smoking may play a role.<sup>13</sup> Pollutants can affect the severity and occurrence of dandruff, and flare-ups are more prevalent under conditions that favor the growth of *Malassezia spp.* including cooler temperatures, low humidity, and lower UV exposure.<sup>14</sup>

The treatment of SD includes a selection of anti-fungal agents to control *Malassezia spp.*, anti-inflammatory compounds, and keratolytics to facilitate the removal of flakes.<sup>15,16</sup> Ketoconazole is a commonly used agent that is fungistatic against *Malassezia spp.* and has been shown to lower the load of *Malassezia spp.* and improve signs and symptoms of SD.<sup>17</sup> Studies have confirmed that both 1% and 2% ketoconazole shampoo are effective for treating dandruff and SD.<sup>18</sup> Selenium disulfide is an effective anti-dandruff ingredient that is fungicidal to *Malassezia spp.*, rebalances the bacterial composition of the scalp, and has

keratolytic effects.<sup>19,20</sup> Previous studies demonstrate that a 1% SeS2 shampoo is as effective as 2% ketoconazole shampoo for treating patients with moderate to severe SSD.<sup>21</sup>

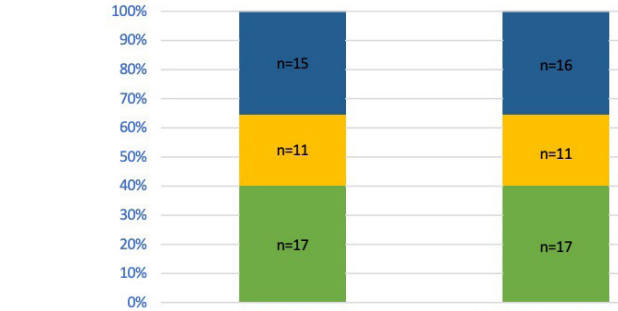
In this study, 0.6% micronized selenium disulfide shampoo (SeS2) (Dercos® anti-dandruff US, Vichy Laboratoires, France) was compared to 2% ketoconazole (Nizoral™ 20 mg/g shampoo, Janssen Pharmaceutica, Belgium NV) for the treatment of moderate to severe SSD. In addition to SeS2, this shampoo includes ingredients to promote the removal of flakes, facilitate barrier repair, hydrate, and soothe the scalp.

## MATERIALS AND METHODS

All subjects provided written informed consent, and the study complied with local legal regulations, good clinical practices, and the principles of the Declaration of Helsinki.

This study was a single-center, 6-week, randomized, double-blind study with 2 parallel groups to compare the benefits and attributes of 2 shampoos on subjects with moderate to severe scalp seborrheic dermatitis. Subjects included men and women with Fitzpatrick skin phototypes III–VI, aged 18–63. Subjects were randomized into 3 sub-groups based on curl type: types I–III, IV–V, VI–VIII. While 8 curl types are defined by this classification, only types II–VII were represented in the study population.<sup>22</sup> Scalp types included dry, normal, and oily. Each curl type and scalp type had a minimum of 2 subjects participating in each product category. A total of 87 patients were enrolled and completed the study. There were 43 subjects in the SeS2 shampoo group (91% female) and 44 subjects in the ketoconazole shampoo group (93% female; Table 1).

TABLE 1.

| Demographics                                                                        |                                                                                      |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 0.6% Selenium Disulfide Shampoo                                                     | 2% Ketoconazole Shampoo                                                              |
| 43 Subjects                                                                         | 44 Patients                                                                          |
| 91% female, 9% male                                                                 | 93% female, 7% male                                                                  |
| 18-57 years old                                                                     | 18-63 years old                                                                      |
| Mean TSS at baseline based on average of 8 zones: 6.2                               | Mean TSS at baseline based on average of 8 zones: 6.2                                |
| Mean SSSD score at baseline: 6.9                                                    | Mean SSSD score at baseline: 6.8                                                     |
| Curl Type Repartition                                                               |                                                                                      |
|  |  |
| 0.6% SeS2                                                                           | 2% Ketoconazole                                                                      |
| ■ I-III ■ IV-V ■ VI-VIII                                                            | ■ Normal ■ Dry ■ Greasy                                                              |

To be included, subjects had to have moderate to severe scales at baseline as determined by the Total Scales Score (TSS). TSS is the sum of adherent and non-adherent scales, with 0=no scales and 5=very large quantity of scales. TSS had to be  $\geq 4$  (ranging from 0 to 10) at baseline with an adherent scales score  $\geq 2.5$  (ranging from 0 to 5) and no limit for non-adherent scales score. The TSS was calculated by taking an average of 8 scalp zones. Subjects were instructed not to use any haircare products, including conditioner, hair masks, non-rinsed hair care products, oil, or anti-scale products for the duration of the study. Styling products were permitted but not within 3 days prior to a study visit, and hair color or bleach could be used, but not within a week of a study visit.

Subjects were excluded if they had used topical or oral corticosteroids, antihistamines, oral or topical anti-fungal medications, non-steroidal anti-inflammatory medications, immunosuppressives, or lithium-based drugs within 4 weeks before entering the study. Oral or topical retinoids could not be used for 6 months prior to the study. Patients with immunosuppressive disorders, severe medical conditions, or those who were pregnant or breastfeeding were excluded. Subjects with alopecia at the vertex (stage > IIIa Hamilton and > I Ludwig) or who had over 60% gray hair were excluded, as these phenotypes could obscure the ability to assess scales.

There was a 2-week washout period where subjects used a specified neutral, non-medicated shampoo three times weekly. On day 0, subjects were randomized to use either micronized SeS2 shampoo 3 times weekly or ketoconazole shampoo 2 times weekly. The frequency and method of product use were selected in compliance with the package instructions for both products. SeS2 shampoo users were directed to wet their hair, then massage the shampoo into the scalp to form a lather. After rinsing, they repeated the application, let it sit for 2 minutes, and rinsed thoroughly again. Ketoconazole shampoo was applied to the hair and scalp, left on for 5–10 minutes, then rinsed.

The investigator evaluated subjects on day -14, 0, 14, and 42. Total Scale Score (TSS) was determined at all time points, including day -14, and Symptomatic Scale of Seborrheic Dermatitis (SSSD) was assessed on days 0, 14 and 42. The SSSD consists of 3 components, including erythema, scales, and pruritus. For each component, the severity ranged from 0 to 5, 0 being the absence of the signs/symptoms and 5 being the most severe form. The SSSD score is the sum of individual scores observed on each component, with a range of 0–15. A mild SSSD score was 0–6, moderate 7–9, and severe 10–15. Clinical assessment of pruritus, as reported by subjects, was conducted at baseline, day 14, and on day 42 with 0=no itching and 5=severe. On day 42, the investigator rated global product satisfaction on a 3-point scale (0=not satisfied and 2=very satisfied) and global efficacy on a 5-point scale (1=worst to 5=complete resolution

or complete remission). Standardized photographs of the most affected zone were taken using LeviaCam at all visits.

The cutaneous acceptability/tolerability evaluation consisted of two complementary phases: the first analyzed the relevant manifestations reported by the subjects in daily logs, and the second analyzed the relevant clinical manifestations observed by the investigator through cutaneous examination. Subjects rated the severity of discomfort (itching, burning, stinging, pruritus) at each visit. A questionnaire concerning efficacy/product satisfaction, tolerability, and cosmesis/acceptability was answered by subjects at all visits. Evaluation of QoL was done using the Scalpdex questionnaire, which consisted of 23 questions that were answered at all time points.<sup>23</sup> These questions were divided into 3 categories, including functioning, emotions, and symptoms, and a total QoL score was calculated.

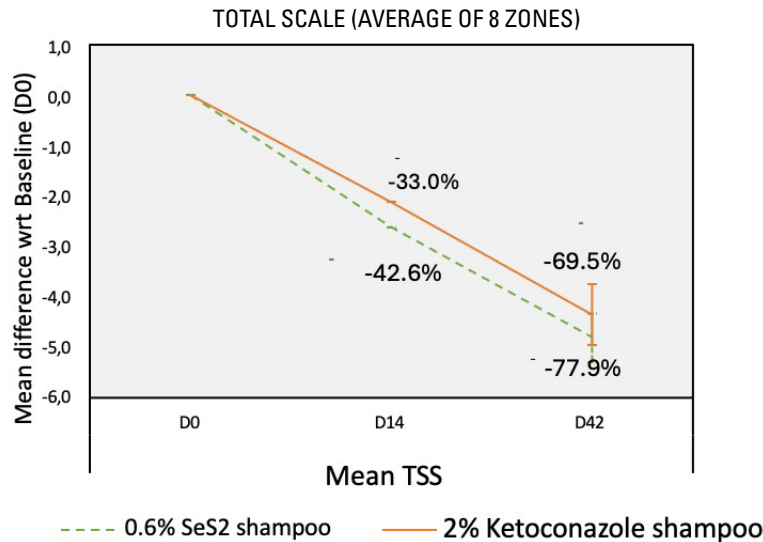
For each parameter and timepoint, the evolution across time with respect to the baseline for each treatment group separately was investigated by using the Student's Paired *t*-test. For each parameter, treatment group comparison, at each time point, was investigated, on the difference data with respect to baseline using the Student's *t*-test for independent data. For parameters where no baseline values are present, the analysis was conducted on the values observed at the specific timepoints, and not on the difference data. *P*-value of < 0.05 was considered significant.

## RESULTS

Table 1 presents the subjects' demographics and baseline assessment. Mean TSS score at baseline, based on the average of 8 zones on the scalp, was 6.2 in both groups. TSS improved with both shampoos over the course of the study, as seen in Figure 1. By day 14, TSS decreased 33.0% in the ketoconazole group and 42.6% in the SeS2 shampoo group (both  $P<0.001$ ). On day 42, TSS decreased 69.5% with ketoconazole and 77.9% with SeS2 (both  $P<0.001$ ). There was no significant difference between groups at any time point. At baseline, average SSSD scores across 8 scalp zones were 6.8 in the ketoconazole group and 6.9 in the SeS2 group. Mean SSSD improved at all post-baseline time points after using both shampoos, as seen in Figure 2. By day 14, SSSD decreased by 27.7% and 34.8%, and on day 42 by 68.0% and 74.5% with ketoconazole and SeS2, respectively (all  $P<0.001$ ). There was no significant difference between the groups at any time point. The severity of all moderate cases improved to mild in both groups. This was also true for one subject with a severe SSSD score at baseline within the ketoconazole shampoo group. Both products show relatively similar evolution over all periods of evaluation, and the micronized SeS2 shampoo was found to be as effective as the ketoconazole shampoo at D14 and D42.

After product application, a significant improvement in the mean 'pruritus severity' score was observed for the average

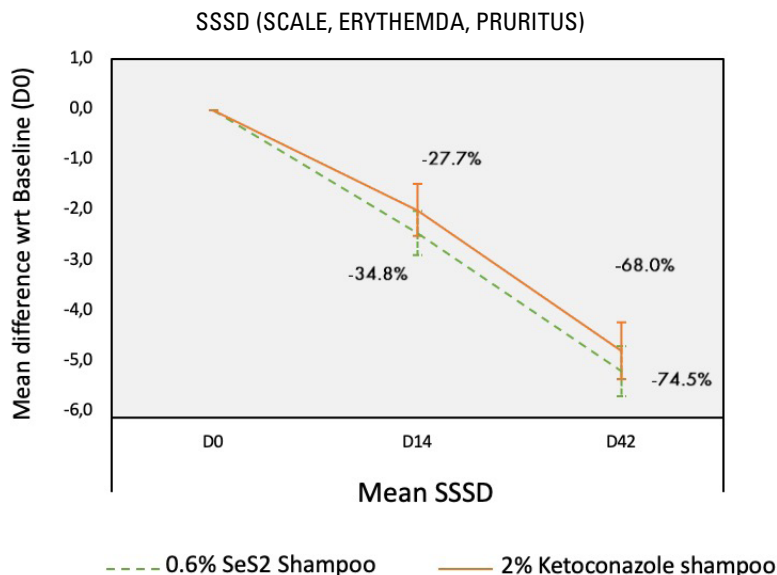
**FIGURE 1.** Both 0.6% and 2% Ketoconazole shampoos demonstrated significant improvement at all post baseline evaluation timepoints ( $P<0.001$  for both) with no significant difference between groups.



of 8 zones for both treatments across all time points. On day 42, pruritus decreased by 67.2% and 75.9% in the ketoconazole and SeS2 groups, respectively (both  $P<0.001$ ; Figure 3). Product comparison revealed no significant difference between the two groups. Global efficacy and satisfaction, as assessed by the blinded dermatologist, showed significant improvement and good satisfaction with both test products (Figure 4).

Subject self-assessment showed itching improved by 76.3% with ketoconazole shampoo and 81% with SeS2 shampoo by day 42 (both  $P<0.001$ ), with no significant difference between groups. Quality of life improved as early as day 14, and on day 42, there was a 67.5% and 70.1% improvement after using the ketoconazole and SeS2 shampoos, respectively (both  $P<0.001$ ; Figure 5). There was no significant difference between treatment groups except "my scalp condition affects the way I wear my hair" on day 14 for the SeS2 shampoo.

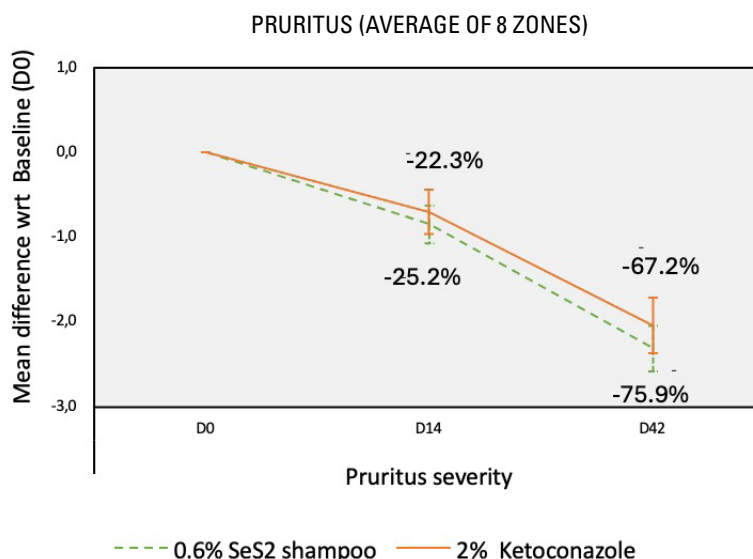
**FIGURE 2.** Both 0.6% SeS2 and 2% Ketoconazole demonstrated significant improvement of all post baseline evaluation timepoints ( $P<0.001$  for both) with no significant difference between groups.



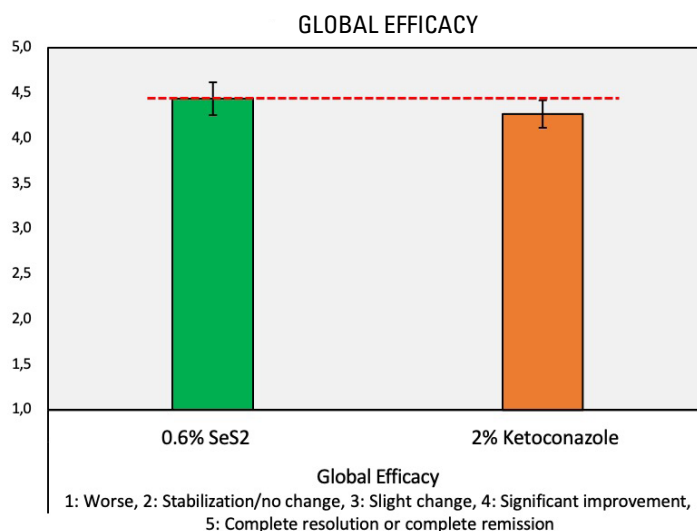
Investigator and subject assessment revealed excellent tolerability with no local discomfort or irritation from either test product. On day 42, overall satisfaction reported by study subjects was 97.7% and 100% for the ketoconazole and SeS2 shampoos, respectively (both  $P<0.001$ ). A subject representing average improvement after using the SeS2 shampoo is seen in Figure 6.

In terms of cosmesis, there was a preference by subjects for the micronized SeS2 shampoo in terms of leaving hair soft, glossy, supple, natural appearing, and that the shampoo was suitable for their hair type. In the SeS2 and ketoconazole groups, respectively, leaves hair soft 98% vs 86%, leaves hair glossy 91% vs 78%, leaves hair supple 95% vs 82%, leaves hair natural appearing 100% vs 91%, and the product is suitable for my hair type 100% vs 87% (all  $P<0.001$ ).

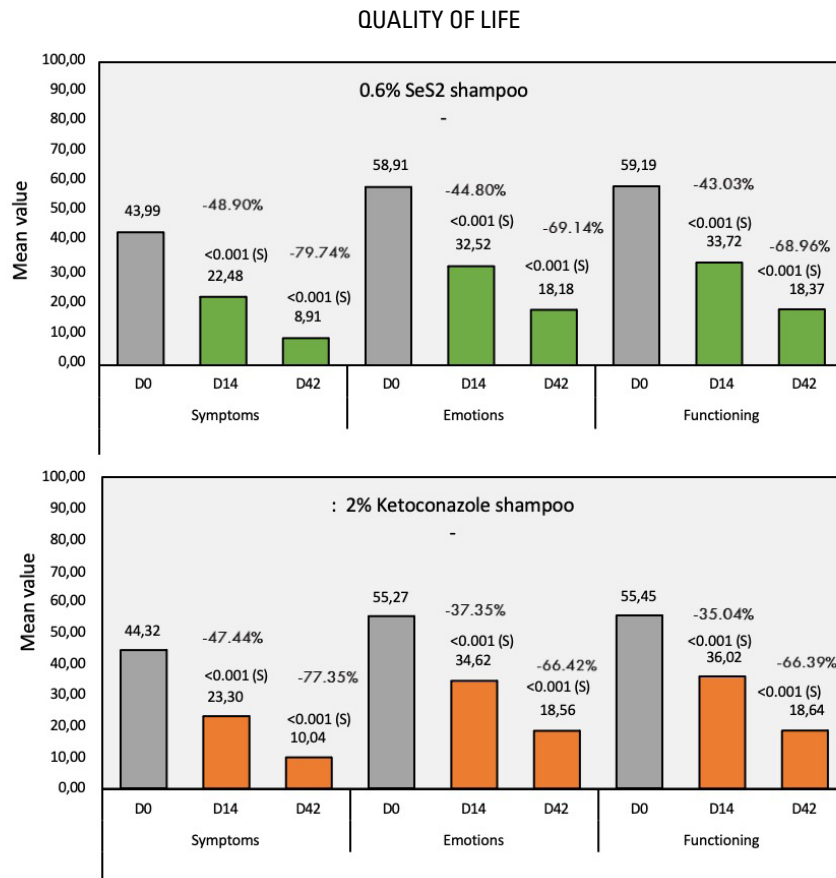
**FIGURE 3.** Both 0.6% SeS2 and 2% Ketoconazole shampoos demonstrated significant improvement at all post baseline evaluation timepoints ( $P<0.001$  for both), with no significant difference between groups.



**FIGURE 4.** Global efficacy and satisfaction as assessed by a blinded dermatologist shows significant global improvement and good dermatologic satisfaction with both 0.6% SeS2 and 2% Ketoconazole shampoos ( $P<0.001$  for both). There was no significant difference between the groups.



**FIGURE 5.** Both shampoos improved symptoms, emotion and functioning from day 14. with no significant difference between treatments except for “my scalp condition affects how I wear my hair” on day 14 for the Ses2 shampoo.



**FIGURE 6.** Clinical images demonstrate noticeable improvement by day 14 with further improvement by day 42 with the use of 0.6% SeS2 shampoo.



## DISCUSSION

Patients with seborrheic dermatitis have a plethora of over-the-counter options from which to choose, including shampoos and leave-in treatments. A common complaint in the dermatologist’s office is that although dandruff treatments are generally effective, many leave hair feeling dry, brittle, and less manageable; this is particularly true of shampoos. In this study, 0.6% SeS2 shampoo was found to be as effective as 2% ketoconazole shampoo for treating moderate to severe

SD. In contrast, study subjects found that the micronized SeS2 shampoo was superior in terms of hair quality and appearance when compared to the ketoconazole shampoo. More subjects felt the SeS2 shampoo left hair soft, glossy, supple, natural appearing, and was suitable for their hair type when compared to the ketoconazole shampoo. Importantly, the SeS2 shampoo was preferred for its cosmetic benefits across curl types. This favorability is an important differentiator that may result in better compliance and improved treatment outcomes.

The efficacy and cosmesis of this SeS2 shampoo can be attributed to its unique formulation. SeS2 itself is a multi-tasking ingredient for treating SSD.<sup>24</sup> It acts to rebalance the scalp microbiome, reducing *Malassezia* spp. and decreasing *Staphylococcus epidermidis* in favor of *Cutibacterium acnes*.<sup>19</sup> SeS2 is cytostatic to the epidermis and reduces epidermal cell turnover, corneocyte production, and flaking.<sup>23</sup> In a comparative study of anti-dandruff shampoos, SeS2 shampoo was found to have the highest keratolytic activity compared to formulations containing zinc pyrithione and ketoconazole.<sup>24</sup> This SeS2 shampoo also contains salicylic acid (SA), providing additional keratolytic effects.<sup>25</sup> SA is lipophilic and readily penetrates the stratum corneum, where it can help dissolve intercellular lipids between corneocytes, helping to loosen scales.<sup>26</sup> SA also has anti-inflammatory activity and may help reduce irritation and mitigate the itch associated with SSD.<sup>27</sup> Niacinamide, or vitamin B3, is an important cosmetic ingredient with diverse skin benefits.<sup>28</sup> It is known to increase ceramide production and strengthen barrier function. Niacinamide reduces oxidative stress, mitigates inflammation, and may improve overall scalp health.<sup>28,29</sup> Glycerin is a potent humectant, helping to moisturize the hair and scalp.<sup>30</sup> Menthol provides a soothing and cooling effect that can reduce inflammation and facilitate healing.<sup>31,32</sup> Thus, this micronized SeS2 shampoo contains carefully curated ingredients to provide a multi-modal approach to treating SSD.

## CONCLUSION

In this study, 0.6% micronized selenium disulfide shampoo was found to reduce the signs and symptoms of moderate to severe scalp seborrheic dermatitis as effectively as 2% ketoconazole shampoo. The SeS2 shampoo was extremely well tolerated and provided superior cosmesis when compared to the ketoconazole shampoo, according to study participants across diverse curl types. The data presented here suggest that this micronized 0.6% SeS2 shampoo should be considered as an alternative to ketoconazole shampoo when treating patients with moderate to severe forms of SSD.

## DISCLOSURES

This study was supported by Vichy Laboratoires. PF, VB, and EH served as members of the Vichy medical advisory board for this publication, and PF provided medical writing services for this manuscript. NK is an employee of Vichy Laboratoires. All authors contributed to the manuscript, reviewed it, and agreed with its contents.

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## AUTHOR CORRESPONDENCE

Patricia K. Farris MD

E-mail:.....pkfarmd@gmail.com

# Objective Measures Needed: Dermatology Program Directors' Perspectives on the USMLE Step 1 Pass/Fail Transition

Om U. Patel MD,<sup>a</sup> Kaitlin G. Burge MD,<sup>a</sup> Ishant S. Yadav MD,<sup>a</sup> William K. Haynes MD,<sup>a</sup> Jason Patel MD,<sup>a</sup> Nicholas J. Van Wagoner MD PhD,<sup>a,b</sup> Lauren C.S. Kole MD<sup>c</sup>

<sup>a</sup>School of Medicine, University of Alabama at Birmingham, Birmingham, AL

<sup>b</sup>Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham, AL

<sup>c</sup>Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL

## ABSTRACT

**Background:** Since January 2022, the United States Medical Licensing Examination (USMLE) Step 1 discontinued reporting a 3-digit score. The objective of this study is to share survey results and to communicate the changes Dermatology residency program directors (PDs) will make to evaluate candidates.

**Methods:** The research team conducted an online survey of PDs and analyzed the responses using R programming and MATLAB scripts. Chi-squared tests were used to identify significant differences in responses to multiple-choice questions, while paired t tests were utilized to compare pre- and post-values for criteria ranking questions.

**Results:** Following the implementation of a pass/fail grading system for Step 1, many PDs will place greater emphasis on Step 2 CK (Clinical Knowledge) scores to differentiate among candidates. Some believe that medical schools should also disclose National Board of Medical Examiners (NBME) shelf exam scores and factor in a student's medical school ranking.

**Conclusion:** The added emphasis on Step 2 CK scores, NBME shelf exam scores, a student's medical institution, and class rank may cloud the positive impacts of this change, providing an opportunity for programs to evaluate students more holistically.

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## INTRODUCTION

The United States Medical Licensing Examination (USMLE) will stop reporting a 3-digit numerical score and begin reporting a pass/fail outcome at the end of January 2022.<sup>1,2</sup> The proposal for this change is to eliminate the major emphasis placed by program directors (PDs) on USMLE performance as a tool for residency screening.<sup>2,3</sup> This change was made to allow medical schools to focus on educating physicians rather than teaching to standardized examinations, allowing PDs to use selection factors that truly represent potential in a given specialty.<sup>4</sup> The purpose of this study was to assess the opinions of Dermatology residency program directors on USMLE examinations' current ability to predict clinical performance and specialty board examination performance, the relative importance of USMLE Step 1 in current selection of residents, and how the change of USMLE Step 1 to pass/fail will change the relative importance of other factors in residency selection.

## MATERIALS AND METHODS

Medical students and physicians at our institution conducted a study to examine the predictive outcomes of the United States Medical Licensing Exam (USMLE) Step 1 transitioning to pass/fail under IRB-300007220 "Predictive Outcomes of USMLE Step

1 Transitioning to Pass/Fail." The study was conducted using an anonymous Qualtrics XM<sup>®</sup> online survey that was distributed via email and through the APD Program Director's listserv for a total of 6 weeks. These respondents were asked to rank 16 different factors, including Step 1 score, in terms of their importance for assessing applicants both before and after the change to a pass/fail system. The factors were ranked on a scale of 1 to 17 (1 being the most important) before the change and 1 to 16 after the change, with Step 1 score being removed as a factor to consider. The factors included in the ranking were: Step 1 score, publications and presentations, research experience, volunteer experience, membership in Alpha Omega Alpha, membership in the Gold Humanism Honor Society, the Dean's letter, personal statement, clerkship grades, preclinical grades, class rank, away rotations, letters of recommendation, graduate degree, Step 2 score, leadership experience, and attendance at a top 40 National Institutes of Health-funded medical school. Custom programming scripts in R and MATLAB were used to analyze the responses, and statistical tests were conducted to determine the significance of the results. Responses were analyzed using nonoverlapping 99.9% confidence intervals, which were used to determine significance for multiple choice questions, and independent t tests were used to analyze ranking questions with significance at  $P < .001$ .

RESULTS

A total of 54 dermatology residency program directors (PDs) out of 149 program directors (36%) completed the survey. When questioned if USMLE Step 1 scores predict a resident's ability to pass their specialty's board exam (Table 1), 50.8% of

PDs answered "Yes" whereas 18.5% answered "No" and 30.8% felt neutral. When asked the same question about USMLE Step 2, 41.5% felt that it did predict ability to pass specialty board exams, while 15.4% ( $P<0.001$ ) felt that it did not. When asked about USMLE Step 1 and its ability to predict clinical

TABLE 1.

| Residency Program Directors' Perspectives on Pass/Fail Scoring of the USMLE Step 1 Exam |                                          |                     |                      |
|-----------------------------------------------------------------------------------------|------------------------------------------|---------------------|----------------------|
| Question                                                                                | Overall<br>% (99.9% confidence interval) |                     |                      |
|                                                                                         | Yes                                      | Neutral             | No                   |
| Do you believe that USMLE STEP 1 scores:                                                |                                          |                     |                      |
| Adequately predict a resident's ability to pass your specialty's board exams?           | 50.8<br>(38.2-63.3)                      | 30.8<br>(20.2-43.6) | 18.5<br>(10.3-30.4)  |
| Accurately predict a resident's ability to perform clinically in your specialty?        | 18.5<br>(10.3-30.4)                      | 20.0<br>(11.5-32.1) | 61.5<br>(48.6-73.1)* |
| Do you believe that USMLE STEP 2 CK scores:                                             |                                          |                     |                      |
| Adequately predict a resident's ability to pass your specialty's board exams?           | 41.5<br>(29.7-54.4)                      | 43.1<br>(31.1-55.9) | 15.4<br>(8.0-26.9)*  |
| Accurately predict a resident's ability to perform clinically in your specialty?        | 30.8<br>(20.2-43.6)                      | 29.2<br>(18.9-42.0) | 40.0<br>(28.3-52.9)  |
| After USMLE STEP 1 becomes pass/fail:                                                   |                                          |                     |                      |
| Should medical schools share clerkship NBME shelf exam scores with residency programs?  | 53.8<br>(41.1-66.1)*                     | 29.1<br>(24.7-34.0) | 11.7<br>(8.8-15.5)   |
| Do you believe students will be better prepared clinically?                             | 6.2<br>(2.0-15.8)                        | 30.8<br>(20.2-43.6) | 63.1<br>(50.2-74.4)* |
| Will a student's medical school rank be considered more?                                | 66.2<br>(53.3-77.1)*                     | 16.9<br>(9.1-28.7)  | 16.9<br>(9.1-28.7)   |

\*An asterisk and bold text indicate a statistically significant ( $P<0.001$ ) plurality of responses by nonoverlapping 99.9% confidence intervals within group.

TABLE 2.

| Relative Rankings by Program Directors of Various Factors Pre and Post Step 1 Pass/Fail |                       |                      |                      |
|-----------------------------------------------------------------------------------------|-----------------------|----------------------|----------------------|
| Variable                                                                                | Pre-Order, Post-Order | Pre-Rank (CI)        | Post- Rank (CI)      |
| Clerkship Grades                                                                        | 2, 1                  | 4.53 (3.71, 5.34)    | 4.10 (3.38, 4.82)    |
| Dean's Letter                                                                           | 6, 5                  | 8.08 (6.90, 9.25)    | 7.23 (6.22, 8.23)    |
| Class Rank                                                                              | 4, 3                  | 6.60 (5.19, 8.01)    | 6.60 (5.29, 7.91)    |
| Letters of Recommendation                                                               | 1, 2                  | 4.20 (3.21, 5.19)    | 4.33 (3.30, 5.35)    |
| Step 2 CK Score                                                                         | 13, 12                | 11.03 (9.54, 12.51)  | 9.23 (7.70, 10.75)   |
| Personal Statement                                                                      | 5, 4                  | 7.18 (5.72, 8.63)    | 7.00 (5.64, 8.36)    |
| STEP 1 Score                                                                            | 3, NA                 | 6.13 (4.71, 7.54)    | NA                   |
| Involvement and Leadership                                                              | 7, 9                  | 8.48 (7.02, 9.93)    | 8.10 (6.66, 9.54)    |
| Volunteering                                                                            | 11, 10                | 9.25 (8.15, 10.35)   | 8.43 (7.29, 9.56)    |
| Gold Humanism Honor Society Membership                                                  | 12, 11                | 9.95 (8.57, 11.33)   | 9.05 (7.74, 10.36)   |
| Alpha Omega Alpha Member-ship                                                           | 9, 8                  | 8.70 (7.17, 10.23)   | 7.88 (6.51, 9.24)    |
| Preclinical Grades                                                                      | 14, 13                | 11.10 (9.94, 12.26)  | 10.23 (9.10, 11.35)  |
| Abstracts, Presentations, and Publications                                              | 8, 6                  | 8.6 (7.46, 9.74)     | 7.58 (6.47, 8.68)    |
| Mean Number of Research Experiences in Specialty                                        | 10, 7                 | 8.9 (7.73, 10.07)    | 7.68 (6.50, 8.85)    |
| Away Rotation in Specialty                                                              | 15, 14                | 11.98 (10.66, 13.29) | 11.78 (10.63, 12.92) |
| Graduate Degree                                                                         | 16, 15                | 13.63 (12.63, 14.62) | 12.58 (11.59, 13.56) |
| Graduated Top 40 NIH Funded School                                                      | 17, 16                | 14.70 (13.54, 15.86) | 14.25 (13.23, 15.27) |

\*An asterisk and bold text indicate a statistically significant ( $P<0.001$ ) plurality of responses by nonoverlapping 99.9% confidence intervals within group.

performance, however, 61.5% ( $P<0.001$ ) of PDs answered “No,” 18.5% answered “Yes,” and 20.0% felt neutral. When inquiring about USMLE Step 2 instead, only 40.0% felt that it was not predictive, while 30.8% felt that it was. The majority of PDs (63.1%,  $P<0.001$ ) also felt that the USMLE Step 1 scoring change would produce less clinically adequate medical students.

To offset the lack of a numerical USMLE Step 1 score, most PDs (53.8%,  $P<0.001$ ) agreed that medical schools should share clerkship NBME shelf exam scores with residency programs. 11.7% ( $P<0.001$ ) of PDs did not agree with this sentiment, and 29.1% ( $P<0.001$ ) felt neutral. 66.2% ( $P<0.001$ ) of PDs also agreed that medical school rank will be more valuable after the scoring transition, although less important than other aspects of the residency application, such as clerkship grades, letters of recommendation, and class rank (Table 2). The mean number of research experiences was ranked higher after the scoring change, although not significantly. Other less important aspects of the application included completing an away rotation in the specialty, having a graduate degree, and graduating from a top-40 NIH-funded school.

## DISCUSSION

According to our survey findings, even after the modification of USMLE Step 1 score reporting, programs will likely still rely heavily on objective measurements. PDs have indicated that Step 2 clinical knowledge (CK) is a suitable alternative, which is supported by our rankings analysis. Recent studies reinforce this trend, revealing that 38.09% of dermatology program directors now place Step 2 CK among their top three selection factors, second only to letters of recommendation and audition rotations.<sup>5</sup> While the intention of this shift was to encourage a more holistic evaluation of dermatology applicants, simply changing the score reporting may not be sufficient to achieve this.

The anticipated focus on Step 2 CK will enable program directors to maintain a standardized test with clear, objective target scores for screening applicants. However, this exam, which is taken at the end of the third year, may delay the stress for students until later in their medical school journey and potentially make it harder for them to prepare a strong application if they do not meet the targeted Step 2 CK score for dermatology. Additionally, this new emphasis on Step 2 CK may exacerbate existing inequalities, particularly as not all medical schools provide equal amounts of dedicated study time or Step 2 preparation resources. These concerns are particularly significant for applicants from osteopathic (DO) and international medical graduate (IMG) backgrounds. A recent national survey found that dermatology program directors believed the Step 1 change would make it even more difficult for DO and IMG applicants to successfully match into dermatology, further emphasizing the need to monitor equity outcomes in future cycles.<sup>6</sup>

Beyond test scores, recent research highlights the rising influence of audition rotations, which have become a key component in applicant evaluation. Audition rotations allow program directors to assess an applicant’s clinical performance, work ethic, and interpersonal dynamics firsthand. In fact, a recent study demonstrated a strong correlation ( $r^2 = 0.817$ ) between the number of audition rotations completed and successful matching at those specific programs.<sup>7</sup> As a result, students are incentivized to complete multiple away rotations, which may impose additional financial and logistical burdens, especially for those from under-resourced backgrounds or institutions without home dermatology programs.

In this evolving landscape, research productivity continues to hold value. Our findings indicated that the number of research experiences, abstracts, posters, and publications was ranked slightly higher after the Step 1 transition, though not significantly. These elements help program directors determine a candidate’s dedication to dermatology and their level of academic engagement. However, similar to clinical experiences, disparities in access to research mentorship—particularly among students without dermatology departments—can further widen the opportunity gap and may lead to more students pursuing gap years to bolster their research credentials.

Clerkship grades and letters of recommendation remain critical factors, consistent with both our survey and recent national data. These components provide essential information on a student’s clinical abilities, professionalism, and work habits across institutions. Yet, while intended to offer objective insight, letters of recommendation, particularly from dermatology faculty, have been shown to sometimes carry limited predictive value or introduce implicit biases. For example, a 2024 study suggested that dermatology PD letters were not necessarily associated with improved match outcomes, suggesting the need for more standardized and transparent assessment tools.<sup>5</sup>

Despite potential disagreement about the alteration in scoring for Step 1, it is our belief that this significant shift offers PDs a chance to re-evaluate how candidates are assessed. However, as the current adjustments indicate, the emphasis has largely shifted rather than dissolved. While the move to pass/fail reporting may support long-term goals of reducing stress and encouraging a broader evaluation of applicants, current adaptations have preserved, and in some cases reinforced, the centrality of numerical and institutional metrics in the dermatology residency selection process.

## CONCLUSION

Our results suggest that in the absence of a 3-digit Step 1 score, program directors have shifted their focus to other objective measures such as Step 2 CK scores, clerkship NBME shelf exam scores, class rank, and letters of recommendation. This pattern

is corroborated by recent national data, which found that over one-third of dermatology program directors now rank Step 2 CK among their top three most important criteria.<sup>5</sup> Similarly, audition rotations have emerged as a dominant evaluative tool, strongly associated with match success.<sup>7</sup> These adjustments reflect a clear continuation of the reliance on quantifiable assessments, despite the elimination of Step 1 numerical scoring.

Although the Step 1 scoring transition was intended to promote holistic review and decrease over-reliance on standardized testing, the resulting selection dynamics suggest a redistribution rather than a resolution of that reliance. Moreover, recent concerns about fairness and equity, particularly for DOs, IMGs, and students from less-resourced institutions, highlight the risk of perpetuating preexisting disparities.<sup>6</sup>

Thus, while our initial data offered a prospective glimpse into how PDs intended to adjust, these recent findings provide a clearer picture of the real-world impact of the Step 1 transition. Future reforms to residency selection should consider these outcomes and strive for a more equitable system that balances objective metrics with qualitative, contextualized evaluations of each applicant's potential.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

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## AUTHOR CORRESPONDENCE

**Om U. Patel MD**

E-mail:..... opatel@uab.edu

# Diagnostic Accuracy and Pitfalls of Publicly Available Artificial Intelligence Models for Nail Disorders

Tanya Boghosian BS,<sup>a</sup> Haroutyun Joulfayan BS,<sup>a</sup> Nazar Boghosian BS,<sup>b</sup>  
Jacob Beer MD,<sup>c,d</sup> Aaron J. Russell MD<sup>e</sup>

<sup>a</sup>Washington University School of Medicine, St. Louis, MO

<sup>b</sup>University of California, Los Angeles, Los Angeles, CA

<sup>c</sup>Beer Dermatology, West Palm Beach, FL

<sup>d</sup>Department of Dermatology and Cutaneous Surgery, University of Miami, Miami, FL

<sup>e</sup>Department of Medicine, Division of Dermatology, Washington University School of Medicine, St. Louis, MO

## ABSTRACT

**Background:** Artificial intelligence is increasingly applied to dermatology, yet its reliability in clinically high-stakes subspecialty domains such as nail disease remains poorly understood. This study evaluated the ability of widely available Vision Language Models (VLMs), ChatGPT-3.5, ChatGPT-4o, and Google Gemini, in diagnosing common nail disorders using clinical images.

**Methods:** A total of 110 clinical images across 11 nail conditions (10 images per diagnosis) were compiled from peer-reviewed sources and confirmed by a board-certified dermatologist. Disorders included infectious, inflammatory, and neoplastic entities. Each VLM was queried with a standardized prompt requesting the top three differential diagnoses and confidence (1–10 scale) for the top choice.

**Results:** Across the models, Google Gemini achieved 34% top-1 accuracy and 51% top-3 accuracy, followed by ChatGPT-4o (33%; 51%) and ChatGPT-3.5 (31%; 45%). VLMs performed best on onychomycosis (sensitivity 0.80; specificity 0.63), green nail syndrome (sensitivity 0.83; specificity 0.98), and onychocryptosis (sensitivity 0.50; specificity 1.00). Furthermore, onychomycosis was the most common incorrect guess across misclassified cases, often appearing as a default diagnosis across a wide range of unrelated presentations. Overall, current VLMs demonstrate poor performance in diagnosing common nail disorders, with moderate accuracy for select conditions, such as onychomycosis. Notably, periungual warts, while frequently encountered in clinical practice, were routinely missed across all models.

**Conclusions:** These findings support the potential role of VLMs as adjunctive tools for pattern recognition but reaffirm that clinical judgment remains essential, especially in cases where diagnostic accuracy has critical implications for patient outcomes.

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## INTRODUCTION

Nail disorders encompass a broad spectrum of infectious, inflammatory, neoplastic, and traumatic conditions that may present with overlapping clinical features. They represent approximately 10% of all dermatologic conditions, accounting for over 21.1 million ambulatory visits in the United States (US) between 2007 and 2016.<sup>1,2</sup> While some entities, such as onychomycosis and onychocryptosis, are frequently encountered in clinical practice,<sup>1</sup> others, such as nail unit melanoma and nail lichen planus, are rare and diagnostically challenging.<sup>3,4</sup> Given their subtle presentations and visual similarity to benign mimics, nail diseases are a known source of diagnostic delay, with potential for significant patient morbidity when malignant or progressive pathology is missed.<sup>3</sup> Even among dermatologists, diagnostic delays are common, driven by limited clinical exposure during training and insufficient confidence in performing nail-specific evaluations and procedures.<sup>5</sup>

Artificial intelligence (AI) has emerged as a promising adjunct in diagnostic medicine. AI-based tools have demonstrated strong performance in specialties such as radiology and ophthalmology, where pattern recognition is central to clinical reasoning.<sup>6</sup> In dermatology, AI has been demonstrated to show a comparable accuracy to dermatologists in diagnosing skin cancer.<sup>7</sup> Applications now extend to teledermatology triage, decision support, and patient education,<sup>8</sup> with public-facing vision-language models (VLMs) like ChatGPT and Gemini broadening access across clinical and consumer settings.<sup>9</sup>

Despite these advances, most dermatologic AI studies have focused on pigmented skin lesions,<sup>7</sup> with limited attention to the nail unit. Nail diseases are structurally and visually distinct from cutaneous lesions, requiring nuanced interpretation of morphology, color, and context. As such, diagnostic accuracy in this domain cannot be assumed based on performance in broader dermatologic tasks. Yet there remains a dearth of

TABLE 1.

| References for Images Used in Model Evaluation |                                                                                                                                                                                                                                                                                                                                                                                                |
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TABLE 1. (CONTINUED)

| References for Images Used in Model Evaluation |                                                                                                                                                                                                                                                                                                                                             |
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literature evaluating AI performance on nail disease, even as publicly accessible VLMs are increasingly used in clinical settings where diagnostic precision is essential.<sup>9</sup>

This study aims to address this critical gap by evaluating the diagnostic performance of three publicly available vision-language models, ChatGPT-3.5, ChatGPT-4o, and Google Gemini, in identifying common nail disorders from clinical images. We provide the first systematic benchmark of VLM accuracy across a broad range of nail diagnoses, assessing top-1 and top-3 accuracy, sensitivity, specificity, confidence calibration, and misclassification patterns, offering insight into the capabilities and limitations of VLMs in nail disease.

## MATERIALS AND METHODS

This diagnostic accuracy study assessed the performance of three publicly accessible vision-language models (VLMs), ChatGPT-3.5, ChatGPT-4o (OpenAI Inc, San Francisco, California), and Google Gemini 2.5 Flash (Alphabet Inc, Mountain View, California), in classifying common nail disorders based on clinical images. The study assessed diagnostic accuracy, confidence calibration, and misclassification patterns using a standardized prompting approach across a curated image dataset.

A total of 110 clinical images representing 11 distinct nail disorders (10 images per condition) were compiled from open-access dermatology resources and peer-reviewed publications, permitting use for academic and research purposes. A detailed list of image sources and references is provided in Table 1. Conditions included infectious (onychomycosis, green nail syndrome, periungual warts), inflammatory (nail psoriasis, nail lichen planus), neoplastic (onychopapilloma, onychomatricoma, nail unit melanoma, Bowen's disease), traumatic (subungual hematoma), and miscellaneous (onychocryptosis) entities. Inclusion required a confirmed diagnosis from the source and clear visualization of the entire nail unit without obstructions. Images were excluded if they were low quality, ambiguous, duplicated, or contained artifacts. Final diagnoses were independently verified by a board-certified dermatologist to ensure case validity.

Each image was uploaded into a new, independent session of each model with the following standardized prompt:

*"Please examine the nail in this clinical image. What are the top 3 most likely diagnoses? List them in order of likelihood. For your top diagnosis, rate your confidence on a scale from 1 to 10."*

No additional information or follow-up was provided. Each model was queried independently, and all outputs, including differential diagnoses and confidence ratings, were recorded verbatim for analysis.

Top-1 and top-3 diagnostic accuracy, defined as the proportion of cases in which the correct diagnosis was listed first or ranked among the top three predictions, respectively, were calculated for each condition across the three models. These values were also averaged across conditions to generate overall accuracy estimates for each model. Diagnoses were considered correct if the model identified the exact disorder or used a general but clinically actionable term that would trigger further workup or referral.

Sensitivity and specificity were computed for each condition within each model. Sensitivity reflected the proportion of correct top-1 predictions for that condition, while specificity reflected the proportion of non-target cases in which that diagnosis did not appear among the top-1 predictions. These values were averaged across models to generate per-condition sensitivity and specificity.

High-confidence errors were defined as incorrect top-1 predictions with a confidence score  $\geq 7$ . Misclassification trends were reviewed descriptively to identify frequently confused conditions and distractor patterns. A misclassification heatmap was generated to visualize top-1 diagnosis output frequencies of all conditions across models.

All images were publicly available, de-identified, and free of personally identifiable information. The study involved no patient contact and no protected health data. As such, it qualified for exemption from institutional review board oversight under federal exemption category 45 CFR 46.104(d)(4).

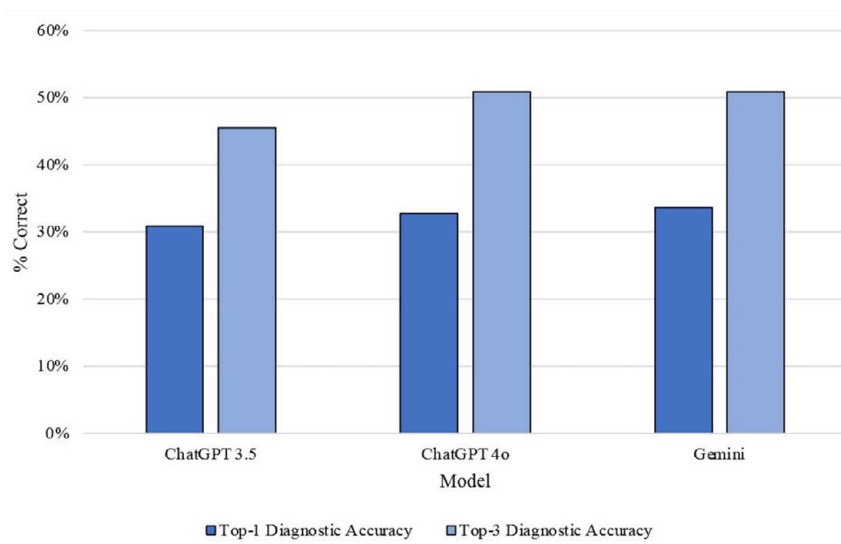
## RESULTS

All three VLMs demonstrated low to modest diagnostic accuracy when tasked with classifying nail disorders from clinical images. Out of 110 total cases, top-1 diagnostic accuracy was highest for Google Gemini (33.6%), followed closely by ChatGPT-4o (32.7%) and ChatGPT-3.5 (30.9%). When considering top-3 predictions, accuracy improved across models, reaching 50.9% for both Gemini and ChatGPT-4o, and 45.5% for ChatGPT-3.5 (Figure 1). Model performance varied widely by disease category.

Infectious conditions were most accurately identified, with green nail syndrome achieving the highest sensitivity across all models (83.3%) and a specificity of 98.3%, followed by onychomycosis (sensitivity 80.0%, specificity 66.3%). Despite being common in practice, periungual warts were not identified by any model (sensitivity 0.0%, specificity 99.7%; Table 2).

Onychocryptosis had 50.0% sensitivity and 100% specificity across all models, while nail psoriasis and nail lichen planus had poor detection rates (sensitivity 23.3% and 0.0%, specificity 97.0% and 99.0%, respectively; Table 2).

**FIGURE 1.** Overall Diagnostic Accuracy of Vision Language Models.



Bars are grouped by VLM model, from left to right: ChatGPT-3.5, ChatGPT-4o, and Google Gemini 2.5 Flash. Each bar is further divided into Top-1 Diagnostic Accuracy and Top-3 Diagnostic Accuracy, with the height of each bar corresponding to the percentage of correct diagnoses.

Nail unit melanoma was correctly identified in 36.7% of cases (specificity 92.7%). Onychopapilloma and onychomatricoma were rarely detected (sensitivity 3.3% each, specificity 100% and 99.7%, respectively), with only one correct identification per diagnosis, both by Gemini. Bowen’s disease was not identified in any case (0.0% sensitivity). Subungual hematoma showed moderate recognition (sensitivity 76.7%, specificity 94.3%; Table 2).

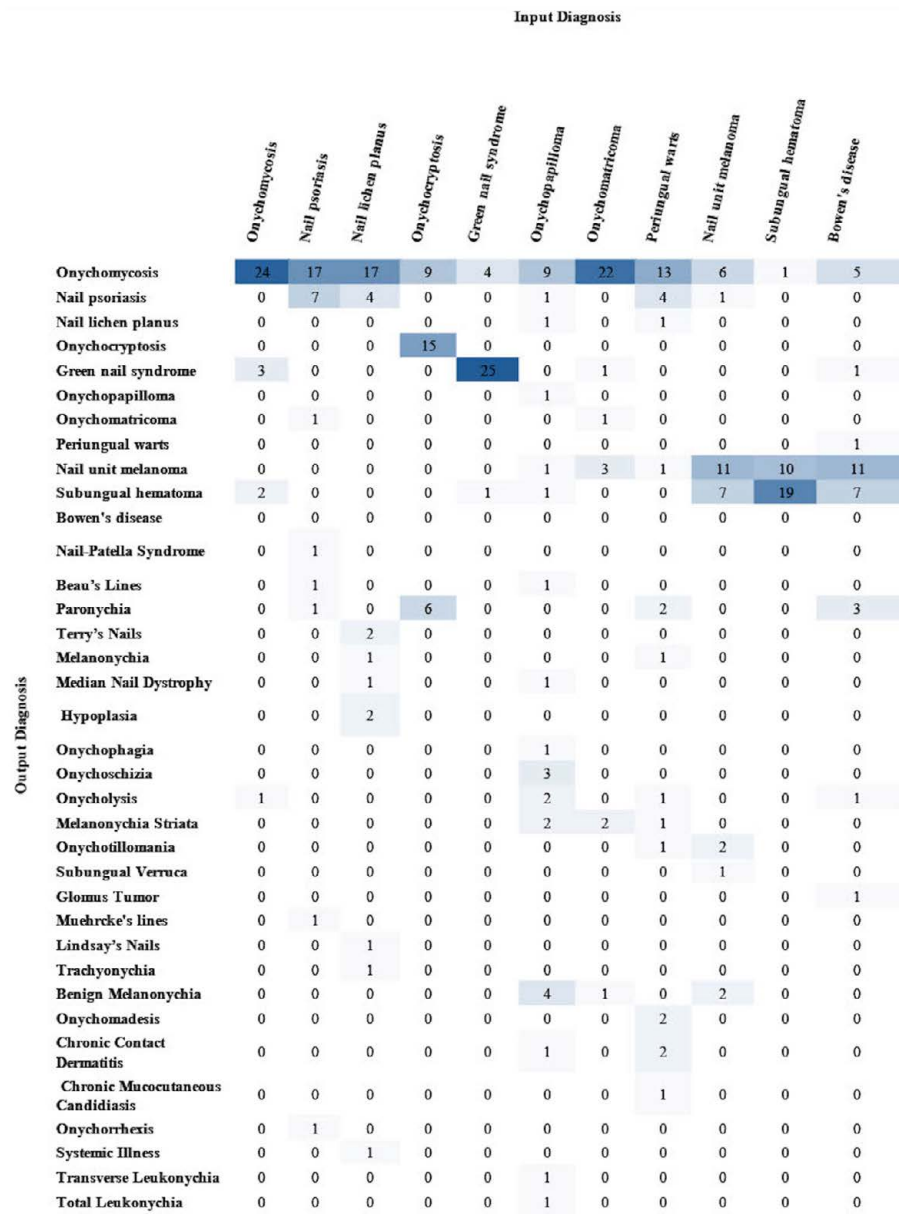
High-confidence errors (confidence  $\geq 7$  with incorrect top 1 diagnosis) accounted for 67.6% of all responses across the three models. A misclassification heatmap is depicted in Figure 2. There was frequent overprediction of common infectious conditions, particularly onychomycosis, instead of less prevalent or visually ambiguous disorders. Rare tumors were often misclassified as benign mimics, such as onychomycosis or subungual hematoma.

**TABLE 2.**

| Sensitivities and Specificities of Vision Language Models (VLMs) |             |             |             |             |               |             |             |             |
|------------------------------------------------------------------|-------------|-------------|-------------|-------------|---------------|-------------|-------------|-------------|
|                                                                  | ChatGPT-3.5 |             | ChatGPT-4o  |             | Google Gemini |             | All VLMs    |             |
|                                                                  | Sensitivity | Specificity | Sensitivity | Specificity | Sensitivity   | Specificity | Sensitivity | Specificity |
| Onychomycosis                                                    | 80.0%       | 69.0%       | 70.0%       | 74.0%       | 90.0%         | 56.0%       | 80.0%       | 66.3%       |
| Nail psoriasis                                                   | 30.0%       | 96.0%       | 30.0%       | 97.0%       | 100.0%        | 98.0%       | 23.3%       | 97.09%      |
| Nail lichen planus                                               | 0.0%        | 100.0%      | 0.0%        | 97.0%       | 0.0%          | 100.0%      | 0.0%        | 99.0%       |
| Onychocryptosis                                                  | 60.0%       | 100.0%      | 20.0%       | 100.0%      | 70.0%         | 100.0%      | 50.0%       | 100.0%      |
| Green nail syndrome                                              | 80.0%       | 99.0%       | 80.0%       | 99.0%       | 90.0%         | 97.0%       | 83.3%       | 98.3%       |
| Onychopapilloma                                                  | 0.0%        | 100.0%      | 0.0%        | 100.0%      | 10.0%         | 100.0%      | 3.3%        | 100.0%      |
| Onychomatricoma                                                  | 0.0%        | 100.0%      | 0.0%        | 100.0%      | 10.0%         | 99.0%       | 3.3%        | 99.7%       |
| Periungual warts                                                 | 0.0%        | 100.0%      | 0.0%        | 100.0%      | 0.0%          | 99.0%       | 0.0%        | 99.7%       |
| Nail unit melanoma                                               | 30.0%       | 93.0%       | 60.0%       | 90.0%       | 20.0%         | 95.0%       | 36.7%       | 92.7%       |
| Subungual hematoma                                               | 60.0%       | 93.0%       | 100.0%      | 96.0%       | 70.0%         | 94.0%       | 76.7%       | 94.3%       |
| Bowen's disease                                                  | 0.0%        | 100.0%      | 0.0%        | 100.0%      | 0.0%          | 100.0%      | 0.0%        | 100.0%      |

Each column contains one of three tested VLMs, followed by the data across all VLMs, in order from left to right: ChatGPT-3.5, ChatGPT-4o, Google Gemini 2.5 Flash, and All VLMs. Each column is further divided into Sensitivity and Specificity for the above parameters. Each row represents one of the 11 nail disorders studied, from top to bottom: onychomycosis, nail psoriasis, nail lichen planus, onychocryptosis, green nail syndrome, onychopapilloma, onychomatricoma, periungual warts, nail unit melanoma, subungual hematoma, and Bowen’s disease.

**FIGURE 2.** Misclassification heatmap of top-1 diagnoses across all vision-language models (VLMs).



Each cell indicates the number of times a diagnosis was assigned as the top-1 output for a given input condition, aggregated across ChatGPT-3.5, ChatGPT-4o, and Google Gemini 2.5 Flash. Only top-1 predictions are shown. Darker shading reflects higher misclassification frequency. Frequent overcalling of onychomycosis and subungual hematoma, and near-complete omission of nail tumors, illustrate key diagnostic limitations.

DISCUSSION

This study investigated the performance of three AI models, ChatGPT-3.5, ChatGPT-4o, and Google Gemini 2.5 Flash, in identifying the most likely diagnosis for a wide range of nail disorders through visual input alone. All models demonstrated minimal diagnostic accuracy, providing correct top-1 diagnoses only in 31–34% of cases, which increased marginally to 46–51% when considering top-3 differential diagnoses. While overall performance was comparable across models, sensitivity values

for individual conditions varied widely (ranging from 0% to 100%). The diagnostic breadth of these models was restricted; they frequently defaulted to onychomycosis and failed to identify rare conditions and nail tumors such as onychopapilloma and onychomatricoma, or even common entities like periungual warts.

VLMs are a subset of Large Language Models (LLMs) that rely on open-source datasets, generating outputs by recognizing

patterns that reflect their training data.<sup>10</sup> This fundamental aspect of VLMs is likely the cause of their underwhelming performance in diagnosing nail disorders in our study, as these diseases represent a rare and visually complex subset of dermatology. Indeed, exploring the metadata of open-source datasets such as ISIC, which contain 550,000 dermatologic images, reveals that none of the images are specific to fingernails or toenails.<sup>11</sup> Prior studies have shed light on the scarcity of publicly available training data, even with the inclusion of widely used datasets such as HAM10000 and BCN20000.<sup>12,13</sup> Given this constraint, the underperformance of VLMs in our study was expected. This limitation also precluded the inclusion of histopathological images, despite their diagnostic value. Some researchers have addressed data scarcity by leveraging private datasets;<sup>14</sup> however, our study prioritized publicly available image collections to better reflect real-world applications accessible to clinicians and general users. Notably, while clinical exposure to nail disorders is also limited during dermatology training, dermatologists consistently outperform VLMs in diagnostic accuracy,<sup>5,7</sup> highlighting the advantage of human clinical reasoning over pattern-based AI, particularly in underrepresented and visually complex conditions.

Previous research assessing AI diagnostic accuracy in dermatology has shown considerable variability. Mevorach et al. utilized a Convolutional Neural Network (CNN) trained on a combination of publicly available and private data, with the model achieving 94% accuracy using images alone.<sup>15</sup> This likely reflects CNNs' specialization in image recognition tasks, enabling superior feature extraction compared to VLMs.<sup>16</sup> However, such CNNs are proprietary and inaccessible to the general public,<sup>15</sup> whereas VLMs are widely available and integrated into most web platforms. Regarding VLMs, Stoneham et al. evaluated ChatGPT-4o on clinical vignettes from 90 dermatology patients, reporting moderate diagnostic accuracy (56%) comparable to generalist physicians. Dermatologists outperformed ChatGPT, achieving a specificity of 83%.<sup>17</sup> Meanwhile, Ahuja et al. demonstrated that ChatGPT-4o identified only 44% of skin disorders correctly when relying solely on images.<sup>18</sup> These results, in addition to our findings, emphasize the indispensable role of clinical context in enhancing AI accuracy and expose the current limitations of VLMs in image-based dermatologic diagnosis.

Despite their low diagnostic accuracy, AI models in our study consistently rated their confidence as  $\geq 7/10$ , reflecting the "hallucination" tendency of LLMs, which includes generating outputs by probabilistic prediction rather than reasoning or fact verification.<sup>19</sup> A prior study evaluating ChatGPT's ability to assess patients based on their Glasgow Coma Scale score, in conjunction with broader contextual factors, found hallucinations up to 40%.<sup>20</sup> We observed similar overconfidence despite zero sensitivity in cases such as nail lichen planus and Bowen's disease. While clinicians also maintain high confidence

despite declining accuracy,<sup>21</sup> they typically recommend further evaluation or referral. In contrast, AI presents outputs as definitive facts, potentially delaying timely diagnosis. This is especially critical for diseases such as nail unit melanoma, where early detection is associated with a 5-year survival rate of 99%, which drops sharply to 35% with delayed diagnosis.<sup>22</sup> These findings highlight the necessity of cautious interpretation of AI-generated diagnoses, even when accompanied by high confidence scores.

Heatmap analysis revealed striking misclassification patterns. Subungual hematoma emerged as a frequent misdiagnosis for cases of nail unit melanoma and pigmented Bowen's disease, reflecting that while models exhibit a rudimentary ability to recognize pigmentation, they lack the diagnostic nuance to distinguish between vascular, melanocytic, and keratinocytic etiologies. Misdiagnosis as a subungual hematoma can hinder timely intervention, particularly since painless subungual hematoma cases are often left untreated.<sup>23</sup> Notably, benign tumors of the nail unit, including onychopapilloma and onychomatricoma, were rarely identified and frequently misattributed to onychomycosis or green nail syndrome, indicating a failure to register nail-specific structural patterns such as longitudinal erythronychia, splinter hemorrhages, onycholysis, and fissuring of the nail plate. Moreover, this suggests a diagnostic default rather than true pattern recognition, which could lead to inappropriate antifungal use or delayed treatment of inflammatory disease. These trends highlight the limitations of current AI models in the nail domain and their potential consequences when applied to clinical decision-making.

While this study provides the first systematic benchmark of VLMs in a wide range of nail conditions, it is limited by the use of isolated clinical images without access to patient history, symptom duration, distribution, or dermoscopic findings. While this reflects real-world use of publicly accessible VLMs, it does not replicate the multimodal data available to clinicians. The dataset included 10 images per condition, which may underrepresent the clinical heterogeneity seen in practice, and although we aimed to standardize image selection, performance may still have been influenced by variability in quality, lighting, and angulation. Additionally, models were not re-prompted or given feedback, though in practice, users may engage in iterative querying to clarify results. Finally, model performance is rapidly evolving, and future updates may alter accuracy.

## CONCLUSION

Despite growing public access to AI tools, current VLMs lack the diagnostic consistency required for accurate nail disease classification. While accuracy was moderate for common infectious and select inflammatory conditions, performance markedly dropped for neoplastic and rare inflammatory

conditions, often with misplaced confidence. Moreover, periungual warts, a common entity in clinical practice, were uniformly missed. While VLMs offer promise as scalable, accessible tools for preliminary pattern recognition, their current performance does not support unsupervised clinical use, particularly in contexts where diagnostic precision is critical.

## DISCLOSURES

The authors declare that they have no conflict of interest.

**Data Availability:** All images used to query VLMs are publicly available on PubMed as publications with Creative Commons licenses allowing the reuse of publication materials with proper attribution. Proper attribution for the images used is provided under Table 1 as citations to the original works.

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## AUTHOR CORRESPONDENCE

**Aaron J. Russell MD**

E-mail:..... aaronrussell@wustl.edu

# Patient Interest in Dermatologists in the United States: A 20-Year Google Trends and Workforce Analysis

Yagiz Matthew Akiska BSE,<sup>a,b</sup> Savanna I. Vidal BS,<sup>a</sup> Mana Nasser BS,<sup>a</sup> Nikita Menta BA,<sup>a</sup> Cleo Whiting MD,<sup>a</sup> Sara Abdel Azim MD,<sup>c</sup> Adam Friedman MD<sup>a</sup>

<sup>a</sup>Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC

<sup>b</sup>Milken Institute School of Public Health, George Washington University, Washington, DC

<sup>c</sup>School of Medicine, Georgetown University, Washington, DC

## ABSTRACT

**Background:** Dermatologists remain unevenly distributed throughout the United States (US), leading to disparities in access to dermatologic care.

**Objective:** To evaluate geographic variation in patient interest in dermatology services and compare it to dermatologist supply to identify areas of potential unmet need.

**Methods:** An ecological, cross-sectional study was conducted using Google Trends data from 2004 to 2023 to assess relative search volume (RSV) for “dermatologist” across US states. RSV was normalized and combined with dermatologist density data from the AAMC to generate a Relative Demand Index (RDI) for each state. Spearman’s rank correlation assessed associations between RDI, dermatologist supply, urbanization, and population size.

**Results:** States with high RDI, such as Alabama and Mississippi, had high patient interest but low dermatologist density, suggesting workforce shortages. Conversely, states like Massachusetts and the District of Columbia had low RDI and high provider density. RDI showed a strong inverse correlation with dermatologist density ( $r_s = -0.76$ ,  $P < 0.0001$ ).

**Limitations:** This study relied on a keyword, Google-only search data, and assumed internet access. County-level nuances were not captured.

**Conclusion:** Significant geographic disparities in dermatologist availability and demand exist, highlighting the need for targeted workforce distribution strategies to ensure equitable access to dermatologic care.

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## INTRODUCTION

In recent years, there has been a notable increase in attention to and financial support for dermatology.<sup>1,2</sup> Skin conditions now rank as the fourth leading contributor to nonfatal disease burden globally, as measured by disability-adjusted life years.<sup>3</sup> Dermatologists play a key role in identifying skin conditions that serve as early indicators of serious health conditions, and are crucial in enhancing the quality of life for patients by addressing the multisystem impacts of various dermatological conditions.<sup>3,4</sup>

Among 84.5 million Americans, a quarter of whom were affected by skin disease, the burden of dermatological conditions on the United States (US) healthcare system incurred \$75 billion in 2013, encompassing medical, preventative, prescription, and non-prescription costs.<sup>5</sup> According to the Association of American Medical Colleges (AAMC), the number of US dermatologists has shown a gradual increase over the past decade, reaching 12,516 in 2019, reflecting an average annual growth of 1.6% since 2010.<sup>2</sup> Yet, the gap between urban and rural areas has widened, with an overall density slightly below the suggested 4.0 per 100,000 population to meet demand adequately.<sup>2,6,7</sup> Despite these projections, dermatologists

continue to be unevenly distributed across the US.<sup>6,7</sup> Findings reported by the US Department of Health and Human Services in 2016 indicated that dermatology is anticipated to be among the medical specialties facing the most significant national deficits by 2025, underscoring the high demand for dermatological care.<sup>8</sup>

When exploring unmet patient needs, quantifying patient demand is essential for identifying actionable healthcare gaps. Google Trends is a platform that compiles and quantifies Google search data, providing population-level insight into search volumes by time and geography.<sup>9</sup> Google Trends has been employed as a proxy to assess patient interest in healthcare services across several medical subspecialties, including orthopedic surgery, ophthalmology, and radiology.<sup>10–15</sup> In the US, 58% of patients self-refer to physicians, often utilizing online resources to do so.<sup>13</sup> Dermatology has been reported to be the most frequently searched medical specialty in the United States, and Google Trends is a powerful tool for estimating patient interest.<sup>13</sup>

To our knowledge, no prior study has analyzed dermatologist supply and patient demand at the state level using Google Trends. This study aims to analyze and compare the density of dermatologists

## MATERIALS AND METHODS

Google Trends search data were analyzed to gauge patient interest in dermatology services across the US. The monthly search volumes for the term "dermatologist" in each state from January 1, 2004, to December 31, 2023, were divided by the total monthly Google searches within that state and averaged. This method yielded a relative value, indicating the search volume for key terms as a percentage of the state's total search volume. The resulting values were normalized on a scale of 0 to 100 to create a Relative Search Volume (RSV) index, to allow for comparisons of searches across states.<sup>16</sup> A higher RSV value suggests greater interest in dermatology, with 100 assigned to the state displaying the highest interest and 0 to the state with the lowest interest.

The number of practicing dermatologists in each state was determined using data from the AAMC's 2023 State Physician Workforce Data Report, which provides information on active physicians per specialty per state.<sup>17</sup> This count was then divided by the 2023 United States Census Bureau state population estimates to calculate the density of dermatologists per 100,000 individuals.

To assess the relative demand for dermatologists across states, a Relative Demand Index (RDI) was utilized, taking into account both supply (physician density per 100,000 people) and demand (RSV) within each state. A demand index (DI) for dermatologists was calculated per state by dividing the RSV by the concentration of dermatologists per 100,000 people. This demand index was normalized on a scale from 0 to 100 by individually dividing each state's DI by the largest DI and multiplied by 100 to create the RDI (Figure 1).<sup>15,18</sup> The RDI can also serve as an indicator of the abundance or shortage of dermatologists in a given state, with a higher RDI suggesting a relative shortage and a lower RDI indicating a relative abundance of dermatologists. This methodology has been employed in similar analyses of RDI in other medical specialties.<sup>11,15,18–20</sup>

The urbanization percentage for each state was determined using data from the United States Census Bureau, which categorizes the total population into urban and rural areas.<sup>21</sup> This involved dividing the population residing in urban areas by the total state population.

**FIGURE 1.** Calculation formula for state-by-state Relative Demand Index.

$$\text{Relative Demand Index} = \text{normalized} \left[ \frac{\frac{\text{Relative Search Volume}}{(\text{No. of Dermatologist in each State} * 100,000)}}{\text{State Population}} \right]$$

All correlation relationships were analyzed via Spearman's rank correlation coefficient. Statistical significance was defined as a *P*-value <0.05.

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.

## RESULTS

### State-by-State Characteristics

Table 1 presents the characteristics of each state, including population size, Google relative search volume, the number of dermatologists, physician density, and urbanization percentage. These variables offer insights into the demand for dermatologists across different regions.

In 2023, 13,133 dermatologists in total were actively practicing in the United States. The overall mean concentration of dermatologists was  $3.68 \pm 1.52$  per 10,000 people, ranging from 10.3 in Washington, DC, to 2.0 in Nevada and Nebraska. By individual states, the highest concentrations of dermatologists per 10,000 people were in Washington, DC (10.3), Rhode Island (7.2), and Massachusetts (7.1), and the lowest concentrations were found in Oklahoma (2.1), Nevada (2.0), and Nebraska (2.0). The mean percentage of the state population living in urban areas was 72.98% and ranged from 100% in the District of Columbia to 35.1% in Vermont.

The mean relative search volume was  $59.33 \pm 14.95$ , with New Jersey (100), Alabama (86), and New York (84) having the highest, and Maine (34), North Dakota (29), and Vermont (28) having the lowest relative search volumes. The states with the highest RDI were Alabama (100), Mississippi (98), and Delaware (92), while the states with the lowest RDI were Vermont (25), Massachusetts (21), and the District of Columbia (21) (Figure 2).

**FIGURE 2.** Map of the United States depicting Relative Demand Index (RDI) by state. Red indicates states with the highest RDI (relative shortage of dermatologists), and green indicates the lowest RDI (relative abundance).

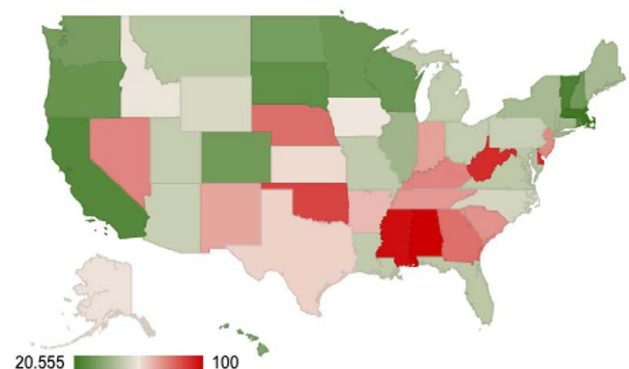


TABLE 2.

| Correlations Between Different State-by-State Characteristics |                      |                        |
|---------------------------------------------------------------|----------------------|------------------------|
| Correlation between Dermatologist Concentration with:         | <i>r<sub>s</sub></i> | <i>P</i><br>(2-tailed) |
| Relative search volume                                        | 0.11                 | 0.43                   |
| Urban population (%)                                          | 0.51                 | 0.00014                |
| Correlation between Relative Demand Index with:               |                      |                        |
| Relative Search Volume                                        | 0.495                | 0.0002                 |
| State Population                                              | 0.034                | 0.78                   |
| Physician Density                                             | -0.76                | <0.0001                |
| Urban Population (%)                                          | -0.27                | 0.05                   |

To compare RDI and population size between states, we categorized them as follows:

- RDI: High (>75th percentile), Moderate (25th–75th percentile), or Low (<25th percentile).
- Population Size: High (>75th percentile), Moderate (25th–75th percentile), or Low (<25th percentile).

Analyzing RDI alongside the state populations revealed diverse patterns, categorized into six categories shared by at least three states, encompassing a total of 50 states and the District of Columbia.

Correlations Between State Characteristics

This study explored correlations between dermatologist concentration and various factors (Table 2). A weak non-significant postive correlation (*r<sub>s</sub>*=0.11, *P*=0.43) was found between dermatologist concentration and relative search volume, while a strong positive correlation was observed with urban population percentage (*r<sub>s</sub>*=0.51, *P*<0.001).

Regarding RDI, a moderate positive correlation (*r<sub>s</sub>*=0.495, *P*=0.0002) with relative search volume suggests increased demand for dermatologists. Conversely, a strong negative correlation was found with physician density (*r<sub>s</sub>*=-0.76, *P*<0.0001), indicating lower demand in areas with higher physician density. Additionally, a moderate negative correlation (*r<sub>s</sub>*=-0.27, *P*=0.05) with urban population percentage suggests lower demand in more urbanized areas.

DISCUSSION

This study examines dermatologist supply and demand in the US, using patient interest as a proxy for need within the context of physician availability. Findings reveal disparities in dermatologist concentration and demand indices across different regions, uniquely considering population size and urbanization.

The relationships between RDI and dermatologist density illustrate the nuanced interplay between dermatologist demand and state populations. States with the highest RDIs, such as Alabama and Mississippi, demonstrate significant demand but

low dermatologist density (<2.6 per 100,000). These states are also less urbanized, indicating limited healthcare infrastructure in rural areas. Conversely, Delaware, despite high urbanization (82.6%), also has a high RDI due to relatively low dermatologist density, highlighting that care gaps exist when the workforce is insufficient.<sup>21</sup> In contrast, states with low RDIs, such as Massachusetts and D.C., benefit from high dermatologist density (>4.0 per 100,000) and urbanization, increasing potential care access. Vermont, with low urbanization (35.1%), also has a low RDI, likely due to lower overall demand and moderate workforce availability (4.6 dermatologists per 100,000).<sup>21</sup> Unsurprisingly, there was a strong negative correlation between dermatologist density and RDI (*r<sub>s</sub>* = -0.76, *P*<0.0001), and higher urbanization was linked to lower RDI, while rural states showed a higher RDI. However, the notable deviations from this generalization provide additional context when discussing dermatologist workforce needs.

Previous analyses showed that 40% of American Academy of Dermatology (AAD) dermatologist members practice in the 100 densest 3-digit postal section codes, with 81% in the Northeastern US and 97% residing in the Boston metropolitan area or in Manhattan.<sup>7,23</sup> The differential distribution is also present in dermatologic subspecialties, with workforce analyses showing that 96% of board-certified pediatric dermatologists and 98% of inpatient dermatologists practice in urban/metropolitan areas.<sup>24,25</sup> While this present analysis focused on trends at the state level, the data from this study further demonstrate the geographic maldistribution of dermatologists.

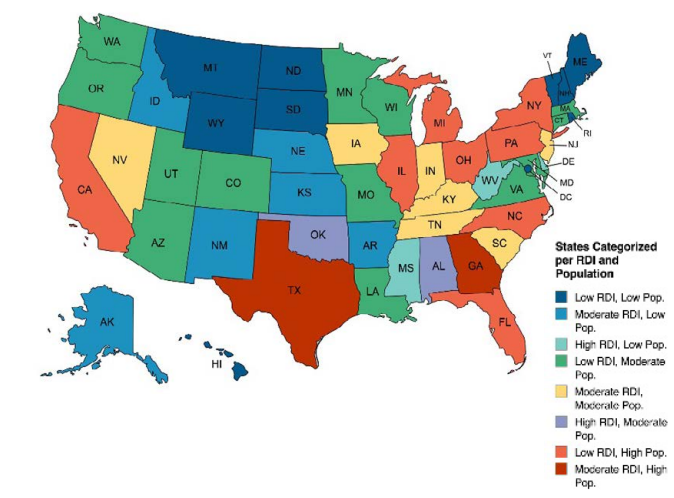
The trends observed in this study align with dermatologists’ perceptions of physician availability. A 2017 AAD Practice Profile Survey revealed that dermatologists in rural communities are most likely to report a need for more dermatologists (48%), whereas urban (39%) and suburban dermatologists (32%) are consistently more likely to report an abundance.<sup>26</sup> These findings support the RDI variations identified in this study, and the persistence of these trends suggests that redistribution efforts, such as incentives for dermatologists to practice in underserved areas or expanded use of teledermatology, are necessary to address differential access.

Regional patterns across the US unveil further workforce imbalances (Figure 3). Rocky Mountain states like Montana, Wyoming, North Dakota, and South Dakota exhibit both low populations and RDIs, whereas neighboring states like Idaho and Nebraska, despite low populations, exhibit relatively higher RDIs (Table 1). The higher RDI in these states may be attributed to a combination of factors, including fewer dermatologists, greater RSVs, and the higher availability of dermatologists in neighboring states, fueling inquiries. Similar trends are seen in the low-population Northeastern states – Vermont, New Hampshire, and Maine. In the Northeast, high-population states

TABLE 1.

| State-by-state Characteristics Population, Search Volume, Dermatologists, and Urbanization, Listed by Decreasing Normalized RDI |                  |                               |                    |                   |              |                                  |                      |
|---------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------------|--------------------|-------------------|--------------|----------------------------------|----------------------|
| State                                                                                                                           | State Population | Google Relative Search Volume | No. Dermatologists | Physician Density | Demand Index | Relative Demand Index Normalized | Urban Population (%) |
| Alabama                                                                                                                         | 5,108,468        | 86                            | 133                | 2.6               | 33.0         | 100                              | 57.7                 |
| Alaska                                                                                                                          | 733,406          | 44                            | 16                 | 2.2               | 20.2         | 61                               | 64.9                 |
| Arizona                                                                                                                         | 7,431,344        | 59                            | 255                | 3.4               | 17.2         | 52                               | 89.3                 |
| Arkansas                                                                                                                        | 3,067,732        | 57                            | 78                 | 2.5               | 22.4         | 68                               | 55.5                 |
| California                                                                                                                      | 38,965,193       | 43                            | 1886               | 4.8               | 8.9          | 27                               | 94.2                 |
| Colorado                                                                                                                        | 5,877,610        | 46                            | 247                | 4.2               | 10.9         | 33                               | 86                   |
| Connecticut                                                                                                                     | 3,617,176        | 79                            | 197                | 5.4               | 14.5         | 44                               | 86.3                 |
| Delaware                                                                                                                        | 1,031,890        | 74                            | 25                 | 2.4               | 30.5         | 92                               | 82.6                 |
| District of Columbia                                                                                                            | 678,972          | 70                            | 70                 | 10.3              | 6.8          | 21                               | 100                  |
| Florida                                                                                                                         | 22,610,726       | 75                            | 1040               | 4.6               | 16.3         | 49                               | 91.5                 |
| Georgia                                                                                                                         | 11,029,227       | 71                            | 294                | 2.7               | 26.6         | 81                               | 74.1                 |
| Hawaii                                                                                                                          | 1,435,138        | 54                            | 64                 | 4.5               | 12.1         | 37                               | 86.1                 |
| Idaho                                                                                                                           | 1,964,726        | 49                            | 49                 | 2.5               | 19.6         | 59                               | 69.2                 |
| Illinois                                                                                                                        | 12,549,689       | 57                            | 501                | 4.0               | 14.3         | 43                               | 86.9                 |
| Indiana                                                                                                                         | 6,862,199        | 57                            | 164                | 2.4               | 23.9         | 72                               | 71.2                 |
| Iowa                                                                                                                            | 3,207,004        | 49                            | 79                 | 2.5               | 19.9         | 60                               | 63.2                 |
| Kansas                                                                                                                          | 2,940,546        | 54                            | 77                 | 2.6               | 20.6         | 62                               | 72.3                 |
| Kentucky                                                                                                                        | 4,526,154        | 67                            | 119                | 2.6               | 25.5         | 77                               | 58.7                 |
| Louisiana                                                                                                                       | 4,573,749        | 74                            | 204                | 4.5               | 16.6         | 50                               | 71.5                 |
| Maine                                                                                                                           | 1,395,722        | 35                            | 33                 | 2.4               | 14.8         | 45                               | 38.6                 |
| Maryland                                                                                                                        | 6,180,253        | 81                            | 305                | 4.9               | 16.4         | 50                               | 85.6                 |
| Massachusetts                                                                                                                   | 7,001,399        | 50                            | 494                | 7.1               | 7.1          | 21                               | 91.3                 |
| Michigan                                                                                                                        | 10,037,261       | 62                            | 370                | 3.7               | 16.8         | 51                               | 73.5                 |
| Minnesota                                                                                                                       | 5,737,915        | 43                            | 233                | 4.1               | 10.6         | 32                               | 71.9                 |
| Mississippi                                                                                                                     | 2,939,690        | 80                            | 73                 | 2.5               | 32.2         | 98                               | 46.3                 |
| Missouri                                                                                                                        | 6,196,156        | 59                            | 220                | 3.6               | 16.6         | 50                               | 69.5                 |
| Montana                                                                                                                         | 1,132,812        | 48                            | 34                 | 3.0               | 16.0         | 48                               | 53.4                 |
| Nebraska                                                                                                                        | 1,978,379        | 54                            | 40                 | 2.0               | 26.7         | 81                               | 73                   |
| Nevada                                                                                                                          | 3,194,176        | 51                            | 64                 | 2.0               | 25.5         | 77                               | 94.1                 |
| New Hampshire                                                                                                                   | 1,402,054        | 45                            | 58                 | 4.1               | 10.9         | 33                               | 58.3                 |
| New Jersey                                                                                                                      | 9,290,841        | 100                           | 370                | 4.0               | 25.1         | 76                               | 93.8                 |
| New Mexico                                                                                                                      | 2,114,371        | 58                            | 52                 | 2.5               | 23.6         | 71                               | 74.5                 |
| New York                                                                                                                        | 19,571,216       | 84                            | 1116               | 5.7               | 14.7         | 45                               | 87.4                 |
| North Carolina                                                                                                                  | 10,835,491       | 68                            | 410                | 3.8               | 18.0         | 54                               | 66.7                 |
| North Dakota                                                                                                                    | 783,926          | 29                            | 20                 | 2.6               | 11.4         | 34                               | 61                   |
| Ohio                                                                                                                            | 11,785,935       | 60                            | 420                | 3.6               | 16.8         | 51                               | 76.3                 |
| Oklahoma                                                                                                                        | 4,053,824        | 61                            | 85                 | 2.1               | 29.1         | 88                               | 64.6                 |
| Oregon                                                                                                                          | 4,233,358        | 39                            | 160                | 3.8               | 10.3         | 31                               | 80.5                 |
| Pennsylvania                                                                                                                    | 12,961,683       | 73                            | 550                | 4.2               | 17.2         | 52                               | 76.5                 |
| Rhode Island                                                                                                                    | 1,095,962        | 62                            | 79                 | 7.2               | 8.6          | 26                               | 91.1                 |
| South Carolina                                                                                                                  | 5,373,555        | 73                            | 159                | 3.0               | 24.7         | 75                               | 67.9                 |
| South Dakota                                                                                                                    | 919,318          | 39                            | 37                 | 4.0               | 9.7          | 29                               | 57.2                 |
| Tennessee                                                                                                                       | 7,126,489        | 69                            | 203                | 2.8               | 24.2         | 73                               | 66.2                 |
| Texas                                                                                                                           | 30,503,301       | 67                            | 970                | 3.2               | 21.1         | 64                               | 83.7                 |
| Utah                                                                                                                            | 3,417,734        | 64                            | 130                | 3.8               | 16.8         | 51                               | 89.8                 |
| Vermont                                                                                                                         | 647,464          | 38                            | 30                 | 4.6               | 8.2          | 25                               | 35.1                 |
| Virginia                                                                                                                        | 8,715,698        | 63                            | 334                | 3.8               | 16.4         | 50                               | 75.6                 |
| Washington                                                                                                                      | 7,812,880        | 43                            | 298                | 3.8               | 11.3         | 34                               | 83.4                 |
| West Virginia                                                                                                                   | 1,770,071        | 69                            | 40                 | 2.3               | 30.5         | 92                               | 44.6                 |
| Wisconsin                                                                                                                       | 5,910,955        | 41                            | 231                | 3.9               | 10.5         | 32                               | 67.1                 |
| Wyoming                                                                                                                         | 584,057          | 53                            | 17                 | 2.9               | 18.2         | 55                               | 62                   |

**FIGURE 3.** State-by-state comparison of relative demand index (RDI) and population (pop.) size in categories of low (<25 %ile), moderate (25–75 %ile), and high (>75 %ile) numbers, respectively. Each state is categorized by low, moderate, or high population size and RDI. The comparison reveals patterns of dermatologist demand relative to population density, helping to identify underserved regions.



like Illinois, Michigan, Ohio, Pennsylvania, and New York showed low RDIs, likely due to their high population, relative physician density, and higher urbanization. Overall, while the calculated RDIs may suggest relatively less demand or a dermatologist abundance in both geographic clusters, it is evident that a maldistribution of dermatologists exists between them.

Limited access to dermatologic care has tangible consequences across several skin diseases, especially amongst rural and other underserved communities, potentially leading to life-threatening consequences for patients.<sup>7,27,28</sup> Higher dermatologist density is associated with lower melanoma mortality rates, while rural areas have higher incidences of late-stage melanoma diagnoses.<sup>29,30</sup> In parallel, greater survival rates for Merkel cell carcinoma have been observed in urban communities.<sup>31</sup> Geographic disparities also impact psoriasis treatment, with increased biologic prescriptions in urban areas.<sup>32</sup> Distinct geographic discrepancies in emergency room visits and prescription medication use in patients with atopic dermatitis were highlighted in one study, noting significant care disparities in the Midwest US.<sup>33</sup> These care access trends, and their consequences, are especially concerning as the prevalence of skin diseases continues to rise.<sup>34</sup>

In high-RDI states with low dermatologist density, primary care physicians (PCPs) often assume dermatologic care responsibilities. One study of 12,000 patients found that skin diseases comprise 12.4% of cases seen by family physicians, and another study showed that only 40% of dermatologic concerns

were evaluated by specialists in underserved areas.<sup>35,36</sup> As a result, non-specialists and PCPs must instead fill that care gap, with one-third of primary care visits addressing a dermatologic concern.<sup>36-38</sup> Although PCPs play a valuable role in addressing basic dermatologic conditions, patients typically report higher confidence in dermatologists managing their care. Additionally, dermatologists’ training better equips them to provide more accurate diagnoses and comprehensive treatment.<sup>37</sup>

Despite a 1.6% annual increase in dermatology residency positions since 2010, workforce distribution remains limited by training site availability and graduate preferences.<sup>39-41</sup> In the Northwest/Midwest cluster, only Nebraska has a residency program, while the Northeast cluster boasts seven to twelve programs per state. This discrepancy highlights the intricate relationship between state population size, RDI, and the availability of dermatology training programs.<sup>41</sup> As dermatologists have been shown to prefer practicing near their training sites, as evidenced by a physician retention rate of 57.1% in the state in which residency was done, the scarcity of dermatologists in low-population states, especially rural regions, is directly linked to the paucity of academic institutions in these regions.<sup>41</sup>

When considering barriers to rural recruitment, urban settings have been shown to align better with the professional and personal preferences of younger dermatologists.<sup>6</sup> Dermatologists also prefer to enter practice in private groups or academic centers and to have opportunities to perform procedural and cosmetic dermatology, all of which are concentrated in urban areas.<sup>2,6,28</sup> These insights may serve as a launching point for longitudinal analyses of specific areas of need and places in which investment in the workforce may be most promising. Strategies to augment the availability of dermatologists in rural areas include promoting recruitment of trainees of rural origin, incorporating rural residency tracks in the residency curriculum, and establishing robust financial incentive programs to draw dermatologists to underserved areas. Of important note, telehealth holds the promise of improving dermatologic access in rural and remote areas. However, the availability of infrastructure needed for telehealth and familiarity with its use pose challenges.<sup>41-48</sup>

Limitations of our study include restricted keyword selection, which may have overlooked relevant terms, the inclusion of only patient-initiated searches, the reliance on internet search data, introducing a potential bias toward individuals with internet access, and the exclusion of other search engines. Lastly, while our state-level estimates fill a knowledge gap, they do not capture nuances at the sub-state, county, or city level due to the lack of a reliable number of dermatologists per state to perform these calculations.

## CONCLUSION

In conclusion, our study provides objective data emphasizing that areas with the greatest demand and the greatest need for dermatologic care are subject to the lowest access. This first-of-its-kind analysis of patient-directed demand and dermatologist resource distribution across states emphasizes the need for tailored strategies to address workforce imbalances. Integrating real-time demand data, like that presented in this study, with workforce planning helps to ensure equitable access to dermatological services. Future research should delve into the factors influencing searches for dermatologist supply and demand and incorporate these data to identify areas of workforce.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

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## AUTHOR CORRESPONDENCE

Adam J. Friedman MD FAAD

E-mail: ..... ajfriedman@mfa.gwu.edu

# Hydroquinone and Emerging Depigmenting Agents: Clinical Guidelines, Regulatory History, and Global Safety Considerations

Mallory A. Von Lotten MS,<sup>a</sup> Aaliyah K. Bourne MPH,<sup>b</sup> Chiemelum Amechi MD,<sup>c</sup> Tiffany T. Mayo MD<sup>c</sup>

<sup>a</sup>Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL

<sup>b</sup>College of Medicine, Florida State University, Tallahassee, FL

<sup>c</sup>Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL

## ABSTRACT

Hydroquinone has long served as the gold standard for hyperpigmentation treatment, but safety concerns, regulatory changes, and growing interest in non-hydroquinone therapies have prompted reevaluation of its role in dermatology. This review outlines the clinical use, safety profile, and evolving regulations surrounding hydroquinone, as well as emerging alternatives and combination therapies. We aim to offer an updated review on best practices for depigmenting treatment protocols and highlight ongoing debates on dermatologic safety and efficacy.

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## INTRODUCTION

**H**yperpigmentation disorders such as melasma, post-inflammatory hyperpigmentation, solar lentigines, and drug-induced pigmentation are common dermatologic complaints, particularly in patients with skin of color. These conditions can have significant psychosocial impacts, such as decreased quality of life and low self-esteem. The mainstay of treatment has historically been topical depigmenting agents, with hydroquinone considered to be the gold standard due to its potent efficacy.<sup>1,2</sup>

However, recent years have seen a rise in safety concerns, regulatory scrutiny, and patient hesitancy regarding hydroquinone use. Known potential adverse effects such as exogenous ochronosis and reports suggesting carcinogenicity in animal studies have fueled concerns.<sup>3,4</sup> This has led to a shift in the therapeutic landscape, prompting increased interest in combination regimens like short-term triple combination therapy (TCT) and alternative agents such as niacinamide, kojic acid, azelaic acid, arbutin, and thiamidol.

This review aims to provide a comprehensive overview of hydroquinone's clinical utility, mechanism of action, safety profile, and global regulatory history. In addition, we explore commonly prescribed combination therapies and evaluate the evidence supporting alternative depigmenting agents, culminating in an updated framework for clinical decision-making in pigmentary disorders.

## Hydroquinone

### *Mechanism, Clinical Use, and Safety Considerations*

Hydroquinone is a reversible inhibitor of tyrosinase, the rate-limiting enzyme in melanin synthesis, and also promotes degradation of melanosomes and melanocytes, leading to skin lightening.<sup>1,5</sup> It is widely used for the treatment of melasma, solar lentigines, freckles, and post-inflammatory hyperpigmentation.<sup>4,5</sup>

The most common acute adverse effect is irritant or allergic contact dermatitis, with post-inflammatory pigmentary change and hypopigmentation also reported.<sup>1,4,5</sup> A rare effect is trimethylaminuria, producing a fish-like odor in sweat, urine, and saliva.<sup>5</sup> Chronic adverse events include nail discoloration, conjunctival melanosis, corneal degeneration, and, most notably, exogenous ochronosis, a gray-blue discoloration associated with high concentrations or treatment durations >1 year, often affecting the cheeks, nose, temples, and neck.<sup>4,6</sup>

To minimize risk, hydroquinone is typically limited to concentrations ≤4%, applied once or twice daily for 2–6 months, with discontinuation if no improvement is observed after 2 months.<sup>3,5</sup> Treatment holidays and concomitant sunscreen use are recommended to reduce photodamage-related recurrence.<sup>3,5</sup> Application should be confined to affected areas, as use on uninvolved skin may cause hypopigmentation. Rarely, distant depigmentation (leukoderma) can occur, particularly in patients of African descent; in such cases, hydroquinone should be stopped immediately and oral corticosteroids considered.<sup>2,5</sup>

### United States Regulatory History and Current Prescription Limitations

In 2006, the US Food and Drug Administration (FDA) proposed that over-the-counter (OTC) hydroquinone products were “not generally recognized as safe and effective” (GRASE), citing rodent carcinogenicity data and clinical reports of ochronosis.<sup>7</sup> Despite this, both OTC (2%) and prescription (4%) formulations remained available until 2020, when the Coronavirus Aid, Relief, and Economic Security (CARES) Act finalized hydroquinone’s classification as a Category II ingredient (not GRASE).<sup>7,8</sup> All OTC hydroquinone products were subsequently withdrawn from the US market by September 23, 2020.<sup>9</sup>

Currently in the United States, although hydroquinone cream is commonly prescribed for treating hyperpigmentation, it is not FDA-approved as standalone monotherapy.<sup>10,11</sup> It is often prescribed as compound formulations, which must carry a disclaimer stating they are not FDA-approved.<sup>10,11</sup> The only FDA-approved hydroquinone-containing agent is Tri-Luma<sup>®</sup>, indicated for the short-term treatment of moderate-to-severe facial melasma.<sup>9,12</sup>

### Carcinogenic Risk Assessment

The potential carcinogenicity of hydroquinone has been primarily raised by rodent studies, where high oral doses were associated with renal tumors in male rats, leukemia in female rats, and hepatic tumors in mice.<sup>13</sup> However, the International Agency for Research on Cancer currently classifies hydroquinone as “not classifiable as to its carcinogenicity to humans” (Group 3), citing inadequate evidence in humans and limited evidence in animals.<sup>13</sup>

Human epidemiologic data, derived largely from occupational cohorts, remain inconclusive: one lithographer cohort reported excess melanoma with only two cases involving hydroquinone exposure, and another photographic processor cohort demonstrated no excess cancer risk with definite exposure.<sup>14</sup> More recently, a 2022 study suggested an approximately threefold increased risk for melanoma and non-melanoma skin cancers with hydroquinone exposure, though these findings require confirmation.<sup>15</sup> Importantly, systemic exposure from topical use is substantially lower than in animal studies, and treatment courses are typically limited to 2–4 months. Within this context, expert consensus supports the safety of hydroquinone when used under medical supervision, while recognizing that additional long-term safety data are needed.

### International Regulatory Perspectives on Hydroquinone

Regulatory frameworks for hydroquinone vary globally, reflecting divergent interpretations of its safety profile. South Africa and several other African nations banned cosmetic hydroquinone use beginning in 1990, with similar restrictions later implemented in multiple countries across the continent.<sup>16</sup> The European Union followed in 2001, banning hydroquinone

from cosmetic products due to risks of exogenous ochronosis and leukomelanoderma.<sup>17</sup>

Australia and Canada have restricted hydroquinone to prescription-only status, with Canada additionally classifying it as “toxic” under the Canadian Environmental Protection Act 1999 and proposing regulation of hydroquinone-containing health products as prescription drugs.<sup>18,19</sup> In contrast, Japan permits hydroquinone in cosmetic formulations under its “quasi-drug” category, allowing concentrations up to 10% since revisions to the Pharmaceutical Affairs Law in 2001.<sup>20,21</sup> These divergent approaches highlight the ongoing tension between safety concerns and ensuring access to effective therapies for pigmentary disorders.

### Triple Combination Therapy (TCT)

#### *Development and Mechanism of Action*

Through research now recognized as unethical, Kligman and Willis developed a formula known as “Kligman formula” containing hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1% in a hydrophilic ointment base.<sup>22</sup> The modern FDA-approved formulation (Tri-Luma<sup>®</sup>) has evolved to include hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% for once daily application to affected facial areas for at least 8 weeks.<sup>12,23</sup>

Hydroquinone functions as a depigmenting agent by inhibiting tyrosinase.<sup>5,23,24</sup> Tretinoin increases cellular turnover, enhances epidermal penetration of hydroquinone, and facilitates pigment elimination while normalizing melanocyte function.<sup>23,25</sup> Fluocinolone acetonide provides anti-inflammatory effects that reduce irritation caused by the other components while potentially decreasing melanin synthesis by inhibiting prostaglandins and cytokines, including endothelin 1 and granulocyte macrophage colony-stimulating factor, which play a role in melanin production.<sup>23,26–28</sup> This multi-modal approach targets multiple pathways in melanogenesis while mitigating individual component side effects, resulting in superior efficacy compared to monotherapy approaches.

### Clinical Efficacy and Comparative Outcomes

Multiple randomized controlled trials and large community-based studies have established that TCT is significantly more effective than hydroquinone monotherapy or dual-combination regimens for the treatment of moderate-to-severe facial melasma.<sup>29–34</sup> Key clinical trials are summarized in Table 1.

### Safety Profile and Long-Term Tolerability

TCT is generally well tolerated, with most adverse events limited to predictable, mild-to-moderate irritation such as erythema, desquamation, burning, and dryness.<sup>29,30</sup> These reactions are typically transient and rarely lead to discontinuation. Long-term safety has been confirmed in a 12-month extension study, which showed sustained efficacy and discontinuation rates of only 1–3%.<sup>35</sup>

TABLE 1.

| Key Clinical Studies of Triple Combination Therapy in Melasma                                                                      |       |           |                                              |                                                        |                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------|-------|-----------|----------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------|
| Safety                                                                                                                             | n     | Duration  | Comparator                                   | Primary Outcome                                        | Results                                                             |
| Taylor et al., 2003<br>(multicenter RCT; moderate-to-severe melasma, mixed ethnicities) <sup>29</sup>                              | 641   | 8 wks     | Dual combinations<br>(HQ+RA, HQ+FA, FA+RA)   | Complete clearing                                      | 26.1%TCT vs 4.6% dual ( $P<0.001$ ).                                |
| "Grimes et al., 2006<br>(community-based phase 4 PIGMENT trial; FST I–VI, multiethnic) <sup>30</sup>                               | 1,290 | 8 wks     | None<br>(community-based;<br>no control arm) | Change in MASI<br>score                                | MASI decreased from 14.68 → 3.64 ( $P<0.0001$ ).                    |
| Chan et al., 2008<br>(multicenter RCT; Asian patients, moderate-to-severe melasma) <sup>31</sup>                                   | 251   | 8 wks     | HQ 4%                                        | Global Severity<br>Score (GSS)                         | 64.2%TCT "none/mild"<br>vs 39.4% HQ ( $P<0.001$ ).                  |
| Nasrollahi et al., 2019<br>(open-label; no comparator arm; Middle Eastern women, mean age 39 yrs) <sup>32</sup>                    | 22    | 8 wks     | None<br>(open-label;<br>no comparator arm)   | Modified MASI<br>(mMASI)                               | mMASI decreased 3.37 → 2.40 ( $P=0.01$ ).                           |
| Cestari et al., 2007<br>(RCT; Brazilian patients with moderate-to-severe melasma) <sup>33</sup>                                    | 120   | 8 wks     | HQ 4%                                        | Investigator's static<br>melasma severity              | 35%TCT vs 5.1% HQ "clear" at week 8 ( $P=0.0001$ ).                 |
| Torok et al., 2005 (multicenter open-label; 12-month extension; mixed ethnicities, mild to severe melasma; FST I–IV) <sup>34</sup> | 228   | 12 months | None<br>(open-label;<br>no comparator arm)   | Investigator static<br>global assessment<br>of melasma | 97% of patients completely or nearly cleared of lesions by month 12 |

TCT = Triple Combination Therapy (HQ 4% + tretinoin 0.05% + fluocinolone acetonide 0.01%, i.e., Tri-Luma formulation unless otherwise noted). HQ = hydroquinone; RA = retinoic acid; FA = fluocinolone acetonide; FST = Fitzpatrick skin type; MASI = Melasma Area Severity Index; mMASI = modified MASI; RCT = randomized controlled trial.

Despite concerns regarding corticosteroid-induced skin atrophy, clinical studies have consistently shown minimal incidence of these complications. A comprehensive histopathological study examining skin biopsies from 62 patients treated with TCT for up to 24 weeks found no statistically significant histopathologic signs of epidermal or dermal atrophy at any time point.<sup>36</sup> Telangiectasia occurrence was also minimal, reported in 1–3% of patients across studies, with most cases being mild and some resolving by study completion.<sup>30,35</sup>

Importantly, safety and tolerability have been consistent across diverse populations. In Asian patients, treatment-related adverse events were reported in 48.8% of TCT patients versus 13.7% with hydroquinone, but these were predominantly mild and did not result in treatment discontinuation.<sup>31</sup> Middle Eastern patients showed similar tolerability, with all adverse events being mild and tolerable.<sup>32</sup>

Limitations and Considerations for Use

Several limitations must be considered when prescribing TCT. Though initial tolerability represents a significant challenge, economic considerations and accessibility issues also create a barrier limiting widespread utilization. The proprietary formulation carries higher costs compared to individual component therapies and may not be universally available or covered by insurance systems.

Recurrence is frequent, with nearly 50% of patients relapsing within 6 months of discontinuation, underscoring the need for maintenance therapy and rigorous photoprotection.<sup>37</sup> Specific contraindications limit patient eligibility, particularly pregnancy and lactation due to tretinoin's teratogenic potential. Additionally, concurrent use of other melasma treatments may be restricted due to increased irritation risk.

Prescription Access and the Rise of OTC Alternatives

Following the reclassification of hydroquinone under the CARES Act, all OTC formulations were removed from the US market.<sup>8,9</sup> While hydroquinone remains available by prescription, most commonly through compounded products or Tri-Luma®, this regulatory change has reduced accessibility for patients without insurance, prescription benefits, or regular dermatologic care.<sup>38</sup> As a result, many individuals with mild-to-moderate hyperpigmentation now rely on non-prescription agents such as azelaic acid, niacinamide, and thiamidol for initial therapy, long-term maintenance, or as adjuncts to prescription regimens. These agents target melanogenesis through complementary mechanisms to combat hyperpigmentation. Early evidence supports the efficacy of thiamidol in melasma and post-inflammatory hyperpigmentation,<sup>39,40</sup> azelaic acid in patients with concurrent acne or rosacea,<sup>41,42</sup> and niacinamide in improving both hyperpigmentation and photoaging-related changes.<sup>38,43</sup>

TABLE 2.

| Comparative Overview of Non-Hydroquinone Depigmenting Agents |                                                                                                          |                                                                                               |                                                                          |                                                             |                                                                     |
|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------|
| Name                                                         | Mechanism of Action                                                                                      | Clinical Use                                                                                  | Side Effects                                                             | Frequency & Duration                                        | Comparison to Hydroquinone 4%                                       |
| Niacinamide                                                  | Inhibits melanosome transfer from melanocytes to keratinocytes; antioxidant effect                       | Topical treatment for hyperpigmentation, anti-aging, and skin barrier improvement             | Generally well tolerated; rare cases of irritation or redness            | Applied once or twice daily; results in 8–12 weeks          | Safer alternative with lower risk of irritation or ochronosis       |
| Kojic Acid                                                   | Inhibits tyrosinase, a key enzyme in melanin synthesis                                                   | Used in creams and serums to treat melasma, sunspots, and post-inflammatory hyperpigmentation | May cause contact dermatitis or skin irritation in sensitive individuals | Applied once or twice daily; results in 8–12 weeks          | Less effective but safer; fewer long-term safety concerns           |
| Arbutin                                                      | Inhibits tyrosinase; antioxidant properties                                                              | Common in over-the-counter skin lightening products; used for melasma and age spots           | Low risk of side effects; occasional mild irritation                     | Applied once or twice daily; results in 8–12 weeks          | Less potent but with a better safety profile                        |
| Azelaic Acid                                                 | Inhibits mitochondrial oxidoreductase and 5-alpha reductase; antimicrobial and anti-inflammatory effects | Treatment for melasma, acne, and rosacea-related hyperpigmentation                            | Mild burning, stinging, or dryness at application site                   | Applied once or twice daily (15–20%); results in 8–12 weeks | Potentially superior MASI reduction; comparable side effect profile |
| Thiamidol                                                    | Potent tyrosinase inhibitor                                                                              | Used in topical products for melasma and facial hyperpigmentation                             | Minimal side effects; occasional irritation or sensitivity reported      | Applied once or twice daily; results in 12–24 weeks         | Comparable efficacy, superiority not statistically confirmed        |
| Tranexamic Acid                                              | Inhibits plasminogen activation; reduces melanocyte stimulation                                          | Used in topical or oral form for melasma and PIH; often in combination regimens               | Mild irritation (topical); risk of thromboembolism (oral)                | Topical: 1–2x daily (2–5%); results in 8–12 weeks           | Emerging alternative; promising for combination therapy             |

Although OTC agents generally act more gradually than hydroquinone, they are well tolerated and safe for long-term use, making them practical choices for maintenance therapy or for patients in whom prescription depigmenting agents are not feasible. In clinical practice, tailoring OTC selection to skin type, sensitivity, comorbid conditions, and patient preference allows for individualized regimens. When combined strategically, these agents can target multiple steps in melanogenesis, thereby enhancing efficacy and addressing the treatment gap left by loss of OTC hydroquinone access.

Non-Hydroquinone Depigmenting Agents

A growing body of evidence supports the efficacy of non-hydroquinone agents for treating hyperpigmentation. The following agents have been most extensively studied and are commonly used as standalone or adjunct therapies:

**Niacinamide (Vitamin B3).** Niacinamide reduces pigment by blocking melanosome transfer and has antioxidant and anti-inflammatory effects.<sup>44,45</sup> Trials show significant lightening within 8–12 weeks.<sup>44</sup> It is widely available, well tolerated, and not linked to ochronosis, making it suitable for long-term or maintenance use.<sup>44,45</sup>

**Kojic Acid.** Kojic acid, a fungal metabolite, inhibits tyrosinase and decreases melanin synthesis.<sup>46</sup> Clinical studies, including hyperspectral imaging, confirm visible pigment reduction.<sup>47</sup> The main limitation is contact dermatitis, but it avoids the severe adverse effects associated with hydroquinone.<sup>47</sup>

**Arbutin.** Arbutin, a glycosylated hydroquinone derivative, inhibits tyrosinase while releasing hydroquinone slowly.<sup>48</sup> Alpha-arbutin is the more effective isomer, improving pigmentation within 2–3 months.<sup>48,49</sup> It is well tolerated with only rare irritation, though less potent than hydroquinone.<sup>49</sup>

**Azelaic Acid.** Azelaic acid inhibits tyrosinase and mitochondrial oxidoreductase and has anti-inflammatory and antimicrobial properties.<sup>50,51</sup> Available in 15–20% formulations, it shows efficacy similar to hydroquinone for melasma while also treating acne and rosacea.<sup>50</sup> Adverse effects are mild, and it is safe for long-term use.<sup>52</sup>

**Tranexamic Acid.** Tranexamic acid (TXA) reduces melanogenesis via plasminogen inhibition and inflammatory mediator suppression.<sup>53</sup> Topical TXA (2–5%) and oral TXA (250 mg twice daily) improve melasma within weeks.<sup>53,54</sup> Topical forms are well tolerated, while oral therapy requires clotting risk assessment.<sup>53</sup>

**Thiamidol (Isobutylamido Thiazolyl Resorcinol).** Thiamidol directly inhibits the active site of tyrosinase, producing rapid improvement in melasma and lentigines within 12–24 weeks.<sup>38,55</sup> Reviews confirm its efficacy and tolerability.<sup>38,55</sup> Comparative studies suggest outcomes similar or superior to hydroquinone, positioning it as a promising emerging agent.<sup>56</sup>

DISCUSSION AND CONCLUSION

Hyperpigmentation is a common concern, particularly in patients with skin of color, where both efficacy and safety are paramount.

Hydroquinone remains the most effective depigmenting agent, yet adverse effects such as exogenous ochronosis and recent regulatory restrictions have limited its role to short, supervised courses.

Triple Combination Therapy (hydroquinone, tretinoin, fluocinolone) is the most efficacious option for moderate-to-severe melasma, with randomized trials confirming superiority over hydroquinone monotherapy. Current recommendations support its use only for short-term regimens, followed by maintenance therapy and strict photoprotection to mitigate corticosteroid-related risks.

Non-hydroquinone alternatives such as niacinamide, kojic acid, arbutin, azelaic acid, and thiamidol are safer for long-term use and can serve as adjuncts or maintenance strategies. However, head-to-head trials and long-term safety data remain limited, and regulatory policies vary globally. Personalized treatment, tailored to skin type, pigmentation severity, and access to care, remains essential. Hydroquinone continues to hold value in clinical practice, but within a broader therapeutic framework that balances efficacy with safety.

## DISCLOSURES

The authors have no conflicts of interest to report.

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## AUTHOR CORRESPONDENCE

Tiffany T. Mayo MD

E-mail:..... tmayo@uabmc.edu

# Exosome-Based Therapies in Dermatology: A Scoping Review

Ou Jia (Emilie) Wang,<sup>a</sup> Barinder (Beenu) Bajwa MD,<sup>b</sup> Jason K. Rivers MD FRCPC DABD FAAD<sup>b,c</sup>

<sup>a</sup>Faculty of Medicine, the University of British Columbia, Vancouver, British Columbia, Canada

<sup>b</sup>Department of Dermatology and Skin Science, the University of British Columbia, Vancouver, BC, Canada

<sup>c</sup>Pacific Derm, Vancouver, BC, Canada

## ABSTRACT

**Background:** In pre-clinical studies, exosomes activate dermal repair mechanisms, and they may show regenerative potential for skin rejuvenation, pigmentation, scarring, hair loss, and inflammatory dermatoses. However, the clinical landscape and its safety remain undefined, despite commercial availability.

**Objective:** To map and summarize clinical studies evaluating exosome-based dermatologic therapies, clarifying evidence, safety, and regulatory context.

**Methods:** A scoping review was conducted in accordance with PRISMA-ScR. Searches of MEDLINE, Embase, CENTRAL, PubMed, US and EU trial registries, and grey literature were performed. Eligible studies involved human participants.

**Results:** Seventeen studies between 2020-2025 were identified, including cohort studies, comparative trials, and case series. Indications included skin rejuvenation, psoriasis, acne scars, and atopic dermatitis. Exosome sources were predominantly mesenchymal stem cell-derived, delivered through topical application, microneedling, fractional CO2 laser, or injection. 76% of studies recorded improvements in wrinkles, pigmentation, elasticity, hydration, or scars. Adverse events were uncommon but included granulomas, necrosis, and allergic reactions post-injection.

**Conclusions:** Exosome-based therapies demonstrate promise for skin rejuvenation and inflammatory dermatoses. Limitations include small sample sizes and short follow-up. Interpretation is further limited by non-randomized, single-arm designs and potential conflicts of interest.

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## INTRODUCTION

Exosomes are extracellular vesicles released by cells that transfer proteins, lipids, mRNAs, and microRNAs to recipient cells playing a role in intercellular communication.<sup>1</sup> Recent studies have highlighted exosomes' role in medical and aesthetic dermatology, where they might contribute to wound healing, pigmentation regulation, scar remodeling, and skin rejuvenation through paracrine signaling and regenerative mechanisms.<sup>2</sup>

To date, the literature on exosome-based therapies has focused on pre-clinical and animal-based studies, and clinical outcomes in humans are limited. This scoping review hopes to address this knowledge gap by evaluating studies that applied exosome-based treatments in humans. By restricting our focus to human studies, we aim to highlight the current clinical landscape, assess therapeutic efficacy, and summarize safety considerations of current exosome preparations.

## MATERIALS AND METHODS

### Protocol and Design

The reporting of this scoping review was conducted in accordance with the Preferred Reporting Items For Systematic

Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) statement.<sup>3</sup>

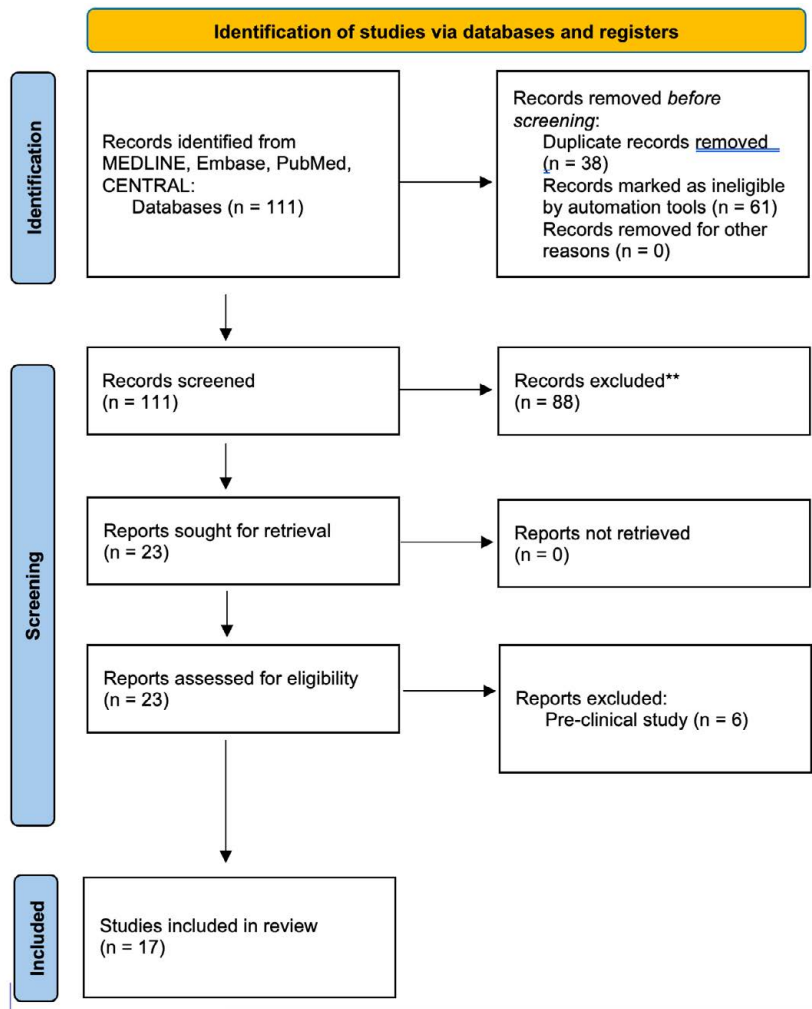
### Data Sources and Search Strategy

A comprehensive literature search was conducted on Dec 21<sup>st</sup>, 2024, across MEDLINE, Embase, and CENTRAL to identify studies evaluating exosome-based therapies for skin rejuvenation, pigmentation, and scar management (Figure 1). The search strategy included a combination of MeSH terms and keywords related to exosomes and extracellular vesicles, skin aging, and dermal remodeling. In June 2025, the search was updated to include studies published between Dec 21<sup>st</sup>, 2024, and June 22<sup>nd</sup>, 2025, and expanded to include case series, case reports, and grey literature sources. Two reviewers independently evaluated titles and abstracts to identify relevant studies (B.B., E.W.) on Covidence. Disagreements were resolved through a consensus process.

### Grey Literature and Trial Registry Search

To capture translational data and to reduce publication bias, we conducted a targeted search of grey literature and clinical trial registries. On June 22, 2025, we queried all entries on ClinicalTrials.gov containing the term "exosomes" and manually

**FIGURE 1.** PRISMA-ScR flow diagram.



PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

screened to identify studies related to skin rejuvenation, wound healing, and hair loss, excluding trials limited to systemic or non-dermatologic indications. A total of 20 relevant studies were identified (Table 1), and selected investigators were contacted for additional information.

A complementary search was performed on the EU Clinical Trials Register on July 27, 2025, using the keyword “exosome” and “exosomes.” Only 21 trials with a EudraCT protocol were returned, none of which were dermatology focused. MedRxiv, BioRxiv, and ProQuest Dissertations & Theses were searched, however no relevant unpublished preprints or preclinical theses with dermatologic endpoints were identified.

**RESULTS**

The initial search yielded 111 articles. After removing 38 duplicates and excluding 61 ineligible studies, 12 articles remained

for full-text review. Seven were excluded (2 being in-vitro studies, 5 being editorials, pre-prints, and conference abstracts). Five studies were thus included. In June 2025, the search was updated to include studies published between December 21, 2024, and July 26, 2025. The inclusion criteria were broadened to consider case series, case reports, and grey literature, and 12 additional studies were added following independent screening for clinical relevance, yielding a total of 17 studies for consideration.

**Study Characteristics**

All studies involved adult participants and were published between 2020 and 2025. Sample sizes in randomized comparative trials included a total of 83 participants, with individual sample sizes ranging between 15 to 28. Ten case series with interventions (including open-label, non-randomized, uncontrolled trials) together enrolled 284 participants, with

TABLE 1.

| Summary of Included Studies and Key Findings |                                                      |                                                                               |                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                       |
|----------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                        | Exosome Source                                       | Study Design                                                                  | Key Findings                                                                                                                                                                                                                                                                                                        | Adverse Effects                                                                                                                                                                       |
| Chandran, 2025                               | Mesenchymal stem cells                               | Open-label, 3 weeks                                                           | No adverse effects. High compliance. No clinically significant changes in inflammatory markers                                                                                                                                                                                                                      | NR                                                                                                                                                                                    |
| Chernoff, 2022                               | Placental mesenchymal stem cells                     | Cohort study, 30 days                                                         | Enhanced skin tone, texture, vascularity, and pigmentation reduction. Synergistic effects with CaHA. Histology showed improved collagen and elastin production                                                                                                                                                      | Mild erythema and edema                                                                                                                                                               |
| Choi, 2024                                   | Unspecified                                          | Case report                                                                   | Foreign body granulomas developed 7 weeks after injection                                                                                                                                                                                                                                                           | Granuloma formation                                                                                                                                                                   |
| Elgueta, 2025                                | Human Wharton's jelly-derived mesenchymal stem cells | 30-day randomized controlled clinical trial in psoriasis                      | Significant reduction in mPASI (33%), plaque size (41%), TEWL (up to 38%), improvement in skin elasticity (43%), safe for use without adverse events                                                                                                                                                                | NR                                                                                                                                                                                    |
| Estupiñan, 2025                              | ADE                                                  | Investigator-blinded, split-face, non-inferiority trial with RF microneedling | Comparable to PRP in improving wrinkling, texture, erythema, and skin quality. Increased collagen I & GAGs histologically                                                                                                                                                                                           | NR                                                                                                                                                                                    |
| Kwon, 2020                                   | ADE gel                                              | Randomized, split-face, 12 weeks                                              | The ADE-treated side showed significant reduction in atrophic scar volume by 32.5% ( $P<0.01$ ). Pore size and roughness reduced ( $P<0.05$ ). Faster recovery time with ADE                                                                                                                                        | Erythema, dryness resolving in 5 days                                                                                                                                                 |
| Majewska, 2025                               | Rose stem cell-derived exosomes                      | Case series                                                                   | Improved healing in burns, scars, dermatitis, and melasma. Improved hydration and skin texture                                                                                                                                                                                                                      | NR                                                                                                                                                                                    |
| Nahm, 2024                                   | Unspecified                                          | Case series                                                                   | Delayed-onset granulomatous reactions (2 weeks - 3 months after injection)                                                                                                                                                                                                                                          | Granuloma formation                                                                                                                                                                   |
| Park, 2023                                   | ADE                                                  | Randomized, split-face, 12 weeks                                              | Wrinkle depth reduced (Ra: 12.4%, $P=0.031$ ). Elasticity increased by 11.3% ( $P=0.002$ ). Hydration improved by 6.5% ( $P=0.037$ ). Reduced melanin index ( $P=0.044$ ). Histopathology showed increased collagen and mucin deposition                                                                            | Transient erythema and petechiae                                                                                                                                                      |
| Peredo, 2024                                 | Placental mesenchymal stem cell-derived              | Case series                                                                   | Accelerated healing post-laser, trauma (dog bite). Reduced erythema, swelling, and scarring                                                                                                                                                                                                                         | NR                                                                                                                                                                                    |
| Proffer, 2022                                | PDE                                                  | Single-arm, non-randomized, 6 weeks                                           | Significant wrinkle reduction across forehead, periorbital, and perioral regions. Significant erythema reduction, brown spots reduction, enhanced luminosity, and improved color evenness. Overall Skin Health Score: 440% improvement ( $P\leq0.0001$ ). Participant satisfaction: 98.2% with minimal side effects | Minimal such as dry skin                                                                                                                                                              |
| Svolacchia, 2024                             | ADE                                                  | Case Series                                                                   | Significant clinical improvements in wrinkle reduction, skin firmness, and hydration after a single mesotherapy session. Confirmed presence of CD81/CD146+ exosomes                                                                                                                                                 | NR                                                                                                                                                                                    |
| Tawanwongsri, 2023                           | Unspecified                                          | Case report                                                                   | Skin necrosis occurred after intradermal injection. Lesions showed vasculitis and eccrine gland necrosis. Histopathology demonstrated leukocytoclastic vasculitis                                                                                                                                                   | Severe pain, erythematous-to-purplish nodules, skin necrosis, post-inflammatory hyperpigmentation and atrophic scarring                                                               |
| Theodorakopoulou, 2024                       | Rose stem cells                                      | Open-label, 12 weeks                                                          | Pigmentation improved: superficial reduced by 13% ( $P<0.001$ ), deep by 16% ( $P<0.001$ ). Wrinkles reduced by 6.3%. Redness and skin quality improved. Significant improvement in DLQI and MELASQoL scores                                                                                                        | Mild erythema, pruritus resolving in 48 hours                                                                                                                                         |
| Wan, 2025                                    | Mesenchymal stem cell-derived                        | Case series                                                                   | 85% showed $\geq 1$ -point improvement in AD severity (vIGA-AD). 50% had $\geq 2$ -point reduction                                                                                                                                                                                                                  | NR                                                                                                                                                                                    |
| Wyles, 2024                                  | PDE                                                  | Prospective, single-arm, evaluator-blinded clinical study, 12 weeks           | Improved skin luminosity, color evenness, pigmentation, and collagen structure                                                                                                                                                                                                                                      | No serious events. Mild dry skin in 16%                                                                                                                                               |
| Zhuang, 2023                                 | ADE                                                  | Case report                                                                   | Swelling significantly reduced post-treatment: forehead swelling resolved in 4 days, and retroauricular lymph node swelling resolved in 8 days. Ultrasound confirmed reduction in soft tissue and nodes.                                                                                                            | Exosome injection caused anaphylaxis. Possible adverse effects from treatment drugs include pigmentation, tissue atrophy (triamcinolone), and ulceration or marrow suppression (5-FU) |

Abbreviations: ADE: adipose-derived exosomes  
PDE: platelet-derived exosomes  
NR: none reported

individual studies ranging from 3 to 72 participants. In addition, three single-patient case reports were identified (Table 2). Most trials were conducted in dermatology or aesthetic clinics from South Korea, the United States, and Europe.

Exosome Source and Delivery

Mesenchymal stem cell-derived exosomes (adipose-, placental-, and Wharton’s jelly-derived) were the most common source of exosomes (n=229).<sup>4-12</sup> Two studies utilized platelet derived exosomes (PDE) (n=112),<sup>13,14</sup> two rose-derived exosomes (n=20),<sup>15,16</sup> while the exosome source was unspecified in nine patients.<sup>17-19</sup> Exosomes were delivered through multiple modalities including topical application (n=160),<sup>9-11,13,14,20</sup> injection-based approaches with mesotherapy (n=82),<sup>7,12,17-19</sup> microneedling (n=55),<sup>4,8,16</sup> topical application after fractional CO2 laser treatment (n=25),<sup>6</sup> a combined topical-injection therapy with calcium hydroxylapatite (CaHA) (n=40),<sup>5</sup> and a heterogenous case series with multiple energy-based treatments (e.g. laser-assisted drug delivery, radiofrequency microneedling, ultrasound, transdermal electroporation) (n=8),<sup>15</sup> summarized in Table 1.

Clinical Indications and Outcomes

Clinical indications predominantly included facial skin aging and rejuvenation (10 studies, n = 288),<sup>4,5,7,8,13,14,16-19</sup> psoriasis

(2 studies, n = 23),<sup>11,20</sup> atrophic acne scarring (1 study, n = 15),<sup>6</sup> atopic dermatitis (1 study, n = 20),<sup>10</sup> wound healing (1 study, n = 3),<sup>9</sup> hair loss (1 study, n =1),<sup>12</sup> and heterogenous indications (1 study, n = 8).<sup>15</sup> Skin rejuvenation focused on a number of factors, with outcomes were assessed using a combination of validated instruments. Thirteen of 17 studies (76%) reported clinical improvements in at least one domain, encompassing either pigmentation, elasticity, wrinkles, scars, hydration, or texture.<sup>4-11,13-16,20</sup> Four studies focused on adverse events or complications.<sup>12,17-19</sup> Skin necrosis and granuloma formation were highlighted in cases involving injected exosomes.

Across the 8 studies focused on reporting rejuvenation outcomes,<sup>4-8,13,14,16</sup> exosome-based therapies consistently demonstrated clinically meaningful improvements across reported domains. PDE showed improvement in wrinkles, pigmentation, and overall skin health within six weeks.<sup>13</sup> Adipose-derived exosomes (ADE), when synergistically combined with microneedling, yielded better outcomes across parameters of wrinkle reduction, hydration, and elasticity compared to microneedling alone.<sup>4</sup> In another microneedling study, rose stem-cell-derived exosomes paired with non-thermal microneedling provided significant improvements in pigmentation and overall skin rejuvenation, along with measurable quality-of-life improvements.<sup>16</sup> A combination of

TABLE 2.

| Evidence Summary Table Based on the Oxford Centre for Evidence-Based Medicine (OCEBM) Quality Rating Scale |                                        |                |
|------------------------------------------------------------------------------------------------------------|----------------------------------------|----------------|
| Study                                                                                                      | Design                                 | Quality Rating |
| Chandran, 2025                                                                                             | Phase 1, open-label trial              | 4              |
| Chernoff, 2023                                                                                             | Case series                            | 4              |
| Choi, 2024                                                                                                 | Case report                            | 5              |
| Elgueta, 2025                                                                                              | Double-blinded RCT                     | 1              |
| Estupiñan, 2025                                                                                            | Investigator-blinded, split-face trial | 1              |
| Kwon, 2020                                                                                                 | Double-blinded, split-face trial       | 1              |
| Majewska, 2024                                                                                             | Case series                            | 4              |
| Nahm, 2024                                                                                                 | Case series                            | 4              |
| Park, 2023                                                                                                 | Split-face RCT                         | 1              |
| Peredo, 2024                                                                                               | Case series                            | 4              |
| Proffer, 2022                                                                                              | Case series                            | 4              |
| Svolacchia, 2024                                                                                           | Case series                            | 4              |
| Tawanwongsri, 2023                                                                                         | Case report                            | 5              |
| Theodorakopoulou, 2024                                                                                     | Case series                            | 4              |
| Wan, 2025                                                                                                  | Case series                            | 4              |
| Wyles, 2024                                                                                                | Case series                            | 4              |
| Zhuang, 2023                                                                                               | Case report                            | 5              |

1. Well-powered randomized clinical trial or systematic review with meta-analysis  
2. Well-designed controlled trial without randomization or prospective comparative cohort trial  
3. Case-control studies or retrospective cohort study  
4. Case series with or without intervention or cross-sectional study  
5. Opinion of respected authorities or case reports

placental mesenchymal stem cell-derived exosomes with dilute CaHA was also synergistic with tissue remodeling and enhanced skin quality.<sup>5</sup> In acne scar management, ADE used alongside fractional CO2 laser accelerated healing while minimizing scarring.<sup>6</sup>

Wrinkle and fine line reduction was reported in 7 of 8 studies, supported by VISIA-CR, PRIMOS, and blinded split-face trials. Both PDE, adipose-derived exosomes (ADE) alone and when combined with CO2 laser showed significant improvements, with one study showing non-inferiority to PRP and histological increments in collagen.<sup>8</sup> Pigmentation and skin tone improved in 6 of 8 studies, with objective reductions in brown spots shown through VISIA, melanin index and more even skin color. Luminosity improved in 6 of 8 studies, elasticity in 6 of 8 (via cutometer or histology demonstrating neocollagenesis), erythema in 5 of 8 studies, and hydration/barrier in 5 of 8 studies as measured by corneometer and histology. Decreased scarring was reported in 1 study, where a combination of ADE and fractional CO2 laser led to a 32.5% reduction in acne scar volume. Composite outcomes including GAIS and patient satisfaction surveys consistently were comparable to, or favoured the exosome-treated side in split-face comparison.<sup>4,6</sup>

In studies that evaluated topical exosome-based therapies for skin rejuvenation, no serious adverse events were reported. Mild and transient erythema, swelling, or dryness was seen in the setting of topical or microneedle-based delivery, but these resolved spontaneously.<sup>4,8,14–16</sup>

In contrast, 4 case series described significant adverse events following intradermal or subdermal injection of exosome products. One reported the appearance of foreign body granulomas seven weeks after a facial injection of mesenchymal-derived exosomes that resolved with the use of corticosteroids.<sup>19</sup> Another documented a case of cutaneous necrosis after the intradermal injection of lyophilized exosomes, with histopathology demonstrating leukocytoclastic vasculitis and eccrine gland necrosis.<sup>17</sup> This patient developed scarring and hyperpigmentation. One described a case series of delayed onset granulomatous reactions occurring 2-12 weeks post-treatment in individuals receiving facial exosome injections.<sup>18</sup> Another noted a case of acute facial swelling and lymphadenopathy within 24-48 hours after the injection of stem cell-derived exosomes for hair loss, demonstrating a localized allergic reaction with lymphadenopathy.<sup>12</sup> This was treated using intralesional 5-fluorouracil and triamcinolone acetonide.

## DISCUSSION

There is a growing interest in exosome-based therapies for dermatologic use.<sup>18</sup> The therapeutic potential of exosomes is supported by a growing body of preclinical evidence. Exosomes

are increasingly recognized as mediators of intercellular communication in tissue repair and inflammation.<sup>21</sup> *In vitro* and *in vivo* studies have shown that mesenchymal and adipose-derived exosomes stimulate fibroblast proliferation, upregulate type I and III collagen synthesis, and additionally promote extracellular matrix (ECM) remodelling, which is central to dermal repair and anti-aging mechanisms.<sup>22,23</sup> Anti-inflammatory and antioxidant properties have also been reported.<sup>24</sup> Exosomes have been shown to reduce oxidative stress, suppress pro-inflammatory cytokines (eg, IL-6, TNF- $\alpha$ ), and inhibit the NLRP3 inflammasome pathway in cutaneous models.<sup>25</sup> Barrier-restoration effects, ceramide synthesis and upregulation of skin hydration markers like aquaporin-3 have been reported both in *in vitro* and *ex vivo* models of aged or damaged skin.<sup>26,27</sup> These mechanisms were reflected, although indirectly, with the observed improvements across skin parameters in the studies we reviewed.

A recent scoping review of exosome-based therapies for hair loss summarized growing interest in the regenerative potential of exosomes while noting the paucity of robust clinical evidence.<sup>28</sup> Despite the likelihood exosomes stimulate dermal papilla cells, promote angiogenesis, and activate hair follicle stem cells, this review only identified nine clinical reports involving 125 patients.

As exosomes are available commercially, we conducted a grey literature search to capture clinical trial data, regulatory agency and additional reports related to potential harms, to provide a more comprehensive and balanced overview of the clinical landscape. As of July 2025, the U.S. Food and Drug Administration (FDA) confirmed that no exosome products are approved for therapeutic use. They are regulated as biological drugs and require either a Biologics License Application or an Investigational New Drug application for legal clinical use. There are greater than 10 direct-to-consumer businesses offering commercial secretomes within the U.S., varying in price points.<sup>29</sup> The agency cautioned against illegal marketing claims and raised concerns over significant safety concerns to the consumer.<sup>30</sup> European, Japanese, and South Korean governing organizations have also withheld formal approval for clinical use of exosomes, treating them as advanced biological products.<sup>31</sup> In both the European Union and the UK, exosome products derived from human sources are regulated under the Advanced Therapy Medicinal Product (ATMP) framework requiring centralized approval by the European Medicines Agency and its Committee for Advanced Therapies within the EU.<sup>31</sup> Human-cell-derived exosomes marketed as cosmetics are explicitly prohibited in cosmetic products under EU Cosmetics Regulation (EC) No. 1223/2009, Annex II, Item 416.<sup>32</sup> There has been no authorization for plant-derived exosome injections as they are not approved ATMPs in Europe.<sup>33</sup>

Similarly, Japan and South Korea have not approved exosomes

to be used therapeutically, although these products are already available commercially. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) have issued detailed regulatory-science evaluations of extracellular vesicle-based therapeutics. These documents emphasize outstanding challenges in manufacturing consistency and safety regulation, concluding that clinical application remains distant and no exosome product is yet approved for therapeutic usage in Japan.<sup>34,35</sup> Despite a lack of approval, physicians in Japan may still provide exosome-based interventions as part of private medical practice, since current laws do not explicitly restrict such use.<sup>36</sup> As of 2025, South Korea’s Ministry of Food and Drug Safety (MFDS) has not approved exosomes as a commercial or licensed therapeutic product, with the “Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products” first established in 2019. Exosome-containing products are commercially available in skincare products marketed as cosmetics, but not therapeutic products. Several brands using human-derived and plant-derived exosomes offer infused serums and boosters directly to consumers.<sup>29</sup> As of January 2025, the MFDS banned cosmetic claims referencing ‘exosomes’, reinforcing the boundary between cosmetic and therapeutic claims (Table 3).<sup>37</sup>

Although positive outcomes have been reported, these studies have several limitations including small sample size, heterogeneity of methodology, and potential publication bias. As mentioned, clinical studies on exosome-based therapies remain limited, with sample sizes ranging from 10 to 72 participants, and with short follow-up periods ranging between 6-12 weeks. These limitations restrict conclusions on the long-term efficacy, and potential systemic adverse effects of exosomes. Across the studies reviewed, there was also heterogeneity in

exosome types (adipose, platelet, placental, rose stem cells), and the exosome delivery modalities, (topical application, microneedling, and combination treatments). When critically appraising these studies, it is important to note that several trials were funded and/or sponsored by biotech companies (e.g. *Rion Aesthetics*, *ExoCoBio*), some with reported conflicts of interest due to authors’ affiliations and consultancy roles. Even one well-known academic center was involved in two studies, one of which reported a vested interest in ownership of Rion, Inc. and Rion Aesthetics, LLC (Table 4).

The fact that four studies reported on the development of skin necrosis, granuloma formation, and allergic reactions following direct exosome injections, emphasized the need for a systematic analysis of safety outcomes.<sup>17,19</sup> Tumour-derived exosomes may contribute to immune evasion through immunosuppressive signals to immune cells.<sup>38–40</sup> Another concern involves the theoretical risk of transmitting latent or adventitious viruses, with exosomes’ endogenous role in facilitating viral communication and immune evasion, as in HIV and HBV.<sup>41–43</sup> GMP-grade manufacturing and donor screening are intended to minimize such risks,<sup>44</sup> typically with viral clearance studies and adventitious agent testing,<sup>45</sup> but cosmetic-grade products may lack safeguards. A recent review assessed a dozen human EV/exosome studies and observed a large variability methodologically along with a mixed adherence to the Minimal Information for Studies of Extracellular Vesicles (MISEV) guidelines as published by the International Society for Extracellular Vesicles (ISEV).<sup>46</sup> Exosomes are used primarily topically, however their ability to penetrate the skin and enter the systemic circulation raises questions about long-term safety.<sup>47,48</sup>

As of March 2025, our review of clinical trial databases such as

**TABLE 3.**  
**International Regulatory Status of Exosome-Based Therapies By Jurisdiction**

| Region         | Regulatory Authority                                                               | Classification                                                                                                                                                                                                          | Approval Status                                                                                                                       | Regulation and Use                                                                                                                                                   |
|----------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Canada         | Health Canada, Biologic and Radiopharmaceutical Drugs Directorate                  | Classified as biologic drugs and subject to New Drug Submission requirements                                                                                                                                            | No exosome-based therapies authorized                                                                                                 | Requires clinical trial authorization. Regulatory framework still emerging                                                                                           |
| United States  | Food and Drug Administration (FDA), Center for Biologics Evaluation and Research   | Classified as biological products and drugs under the FD&C and PHS Acts                                                                                                                                                 | No exosome-based therapies approved. Require Biologics License (BLA) or Investigational New Drug (IND) for clinical use               | Subject to Current Good Manufacturing Practice. Pre-market review required. FDA has issued public safety warnings against unauthorized exosome therapies             |
| European Union | European Medicines Agency                                                          | Classified as Advanced Therapy Medicinal Products if containing functional RNA. Human-cell-derived exosomes prohibited in cosmetic products under <i>EU Cosmetics Regulation (EC) No. 1223/2009, Annex II, Item 416</i> | No exosome-based therapeutics approved                                                                                                | Regulatory pathways established under stem cell and gene therapy frameworks                                                                                          |
| Japan          | Ministry of Health, Labour and Welfare. Pharmaceuticals and Medical Devices Agency | Regenerative medicine if containing living cells. Otherwise classified as biologics or medications                                                                                                                      | No exosome therapies approved. However physicians may provide exosome treatments in self-funded private medical practice, unregulated | Classification depends on cell viability. Limited formal approval pathways                                                                                           |
| South Korea    | Ministry of Food and Drug Safety (MFDS)                                            | Classified as biologics                                                                                                                                                                                                 | No formally approved exosome-based medical products. Since 2025, marketing claims referencing ‘exosomes’ have been restricted by MFDS | Exosome-containing cosmetics (e.g. Exomide, Exocoon) commercially available but not authorized therapeutics. Regulatory approval for therapeutic use remains pending |

TABLE 4.

| International Regulatory Status of Exosome-Based Therapies By Jurisdiction |                                                      |                                                                                                 |                                                                                                                   |                                                                                                                                                        |                                                  |
|----------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Study                                                                      | Exosome Source                                       | Funding Source                                                                                  | Manufacturer                                                                                                      | Declared Conflicts of Interest                                                                                                                         | Study Design                                     |
| Chandran, 2025                                                             | Mesenchymal stem/stromal cells                       | Paracrine Therapeutics and Industry Alignment Fund - Pre-Positioning Programme (IAF-PP) Funding | Not sourced from a commercial supplier                                                                            | Multiple authors are employees of Paracrine Therapeutics                                                                                               | Single-arm, non-randomized                       |
| Chernoff, 2022                                                             | Placental mesenchymal stem cell exosomes             | Merz-funded JOCD supplement                                                                     | Kimera Labs                                                                                                       | None                                                                                                                                                   | Single-arm, non-randomized                       |
| Choi, 2024                                                                 | Unspecified                                          | None                                                                                            | None declared                                                                                                     | None                                                                                                                                                   | Case report                                      |
| Elgueta, 2025                                                              | Human Wharton's Jelly-derived mesenchymal stem cells | Chilean National Research and Development Agency Grant                                          | Cell Therapy Center, Universidad de los Andes, Chile                                                              | None                                                                                                                                                   | Single-arm, non-randomized                       |
| Estupiñan, 2025                                                            | Adipose-derived stem cell exosomes                   | Funded in part by a research grant to Schweiger Dermatology from Benev Company Inc.             | Exosome Regenerative Complex and the EXO BALM by BENEV (BENEV Company Inc., Mission Viejo, CA).                   | None                                                                                                                                                   | Investigator-blinded, non-randomized, split-face |
| Kwon, 2020                                                                 | Adipose-derived stem cells exosomes                  | ExoCoBio Inc.                                                                                   | SC-CM by ExoSCRT™ technology (ExoCoBio Inc., Seoul, Republic of Korea)                                            | None                                                                                                                                                   | Double-blind, randomized, split-face             |
| Majewska, 2025                                                             | Rose stem cell-derived exosomes                      | None                                                                                            | ASCEplus Derma Signal Kit/SRLV, ExoCoBio Inc., Seoul, South Korea                                                 | None                                                                                                                                                   | Single-arm, non-randomized                       |
| Nahm, 2024                                                                 | Unspecified                                          | None                                                                                            | None                                                                                                              | None                                                                                                                                                   | Case series                                      |
| Park, 2023                                                                 | Adipose-derived stem cell exosomes                   | National Research Foundation of Korea                                                           | ExoCoBio Inc., Seoul, Republic of Korea                                                                           | None                                                                                                                                                   | Randomized, split-face                           |
| Peredo, 2024                                                               | Placental mesenchymal stem cell-derived              | Exocel Bio.                                                                                     | Exovex™, Exocelbio, Doylestown, PA                                                                                | Multiple authors affiliated with Exocel Bio.                                                                                                           | Case series                                      |
| Svolacchia, 2024                                                           | Adipose-derived stem cell exosomes                   | None                                                                                            | Autologous adipose-derived exosomes isolated via the Skin-B® protocol. Not sourced from a commercial manufacturer | None                                                                                                                                                   | Single-arm, non-randomized                       |
| Tawanwongsri, 2023                                                         | Unspecified                                          | None                                                                                            | Manufactured in Korea, no further details supplied                                                                | None                                                                                                                                                   | Case report                                      |
| Theodorakopoulou, 2024                                                     | Rose stem cells exosomes                             | None                                                                                            | ExoCoBio, South Korea                                                                                             | Authors affiliated with ExoCoBio, Allergan, Galderma, Merz                                                                                             | Single-arm, non-randomized                       |
| Wan, 2025                                                                  | Mesenchymal stem cell-derived                        | None                                                                                            | ZISHEL XOMAGE (Zishel Bio Inc., Seoul, South Korea)                                                               | None                                                                                                                                                   | Single-arm, non-randomized                       |
| Wyles, 2024                                                                | Human platelet-derived extract                       | None                                                                                            | Rion Aesthetics, Inc., Rochester, MN                                                                              | Author acts as consultants for Rion Aesthetics, LLC., with co-author and Mayo Clinic having ownership interest in Rion, Inc. and Rion Aesthetics, LLC. | Single-arm, non-randomized                       |
| Zhuang, 2023                                                               | Adipose-derived stem cells-derived exosomes          | None                                                                                            | None                                                                                                              | None                                                                                                                                                   | Case report                                      |

ClinicalTrials.gov and the European Union (EU) Clinical Trials Register revealed no negative or unpublished studies about dermatological applications. There is a clear need for non-industry funded research in the emerging field of exosomes.

Extracellular vesicles degrade quickly under improper storage conditions,<sup>49</sup> with the development of ring-like and cristae-like membranous and structural changes when stored in standard phosphate-buffered saline, as compared to sucrose-based cryoprotective buffers. This underscoring the need for

consistent and standardized manufacturing processes.<sup>50</sup> Finally, it is important to know that when exosomes are derived from monocytes, they may induce vascular inflammation when exposed to an inflammatory stimulus.<sup>51,52</sup>

CONCLUSION

Based on this scoping review, exosome-based therapies demonstrate early promise in regenerative and aesthetic dermatology, as clinical data supports their use for dyschromia, skin aging, and scars, although adverse reactions remain a

concern despite general safety. Study heterogeneity, short term follow-up, and limited safety data indicates that further studies are needed to better inform clinicians on the utility of exosomes. With standardization, regulatory clarity, better manufacturing techniques, and more rigorous clinical trials, exosomes could become a safe and consistent option in both aesthetic and medical dermatology.

## DISCLOSURES

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#### AUTHOR CORRESPONDENCE

Jason Rivers MD FRCPC DABD FAAD

E-mail: ..... jason@pacificderm.ca



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# The Dermoepidermal Junction as the Initiation Point for Reversal of Dermatoporosis

Alan D. Widgerow MBBCh MMed FCS FACS,<sup>a</sup> Orit Markowitz MD,<sup>b</sup>  
Jean Carruthers MD FRCSC FRC (Ophth),<sup>c</sup> Faiza Shafiq MBBS CCRP<sup>a</sup>

<sup>a</sup>Galderma Laboratories, L.P., Dallas, TX

<sup>b</sup>Markowitz Medical, New York, NY

<sup>c</sup>Department of Ophthalmology, University of British Columbia, Vancouver, Canada

## ABSTRACT

**Background:** Dermatoporosis (DP) or chronic cutaneous fragility syndrome has traditionally been linked to extracellular matrix (ECM) dehydration, reduced cellular turnover, epidermal thinning, and vascular fragility. However, recent imaging methods and clinical evidence indicate that the dermoepidermal junction (DEJ) might be the earliest change reflecting DP reversal.

**Objective:** To propose a new mechanistic process in which the DEJ acts as the initiation point for reversing the DP. The process is supported by clinical and imaging evidence, as well as independent literature on DEJ biology.

**Methods:** A combination of clinical and investigational findings, published theoretical models, and evidence from wound-healing, skin-longevity reports, ex vivo model analyses, and device-based interventions formed the basis for the scientific narrative.

**Results:** Cumulative evidence suggests that an initial change in the DEJ, along with structural restoration, appears to trigger or initiate regenerative processes in the ECM and epidermis. These include the renewal of basal stem cells following adhesion signaling in the basement membrane; ECM remodeling through improved communication between the dermis and epidermis, along with enhanced fibroblast interactions involving collagen and elastin; and finally, ECM remodeling and stabilization of basement membrane anchoring provides support and stability to blood vessels, protecting them from recurrent injury.

**Conclusion:** The DEJ acts as a bridge between the epidermis and dermis, providing structural support while also triggering signaling cascades that promote a regenerative environment, contributing to DEJ reversal. Targeting the DEJ could be a logical therapeutic approach, establishing a new paradigm for biomarker analysis and an intervention site for regenerative initiation.

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## INTRODUCTION

Dermatoporosis is a term first coined by Kaya and Saurat in 2007, describing progressive skin thinning, extracellular matrix (ECM) degradation, vascular fragility with resultant purpura, and general vulnerability of the skin.<sup>1</sup> The condition likely affects the vast majority of the population, but it usually manifests in the older age group, typically those over 65 years old. It is underrecognized and may be regarded as the equivalent of “osteoporosis of the skin”, often starting decades earlier than the manifestation seen in older age groups.

Traditionally, the pathogenesis was regarded as one of ECM deficiency, particularly related to glycosaminoglycans (hyaluronic acid in particular), with decreased cellular turnover.<sup>2</sup> More recently, DP has been recognized as associated with a more extensive global ECM degradation, fibroblast senescence, and macrophage dysfunction.<sup>3</sup> This ECM degradation affects the structural support of the vasculature, making it more vulnerable to damage and injury.<sup>3</sup>

A recent clinical trial evaluating regenerative peptides with ECM remodulating activity and marked clinical improvement has demonstrated that the earliest measurable changes appear to be observed in structural changes to the dermoepidermal junction (DEJ), which precede widespread regenerative changes in the ECM and dermis.<sup>4</sup> This suggests that the DEJ, rather than being a passive basement membrane providing structural support, may well signal and initiate the regenerative changes seen with DP reversal.

### The Dermoepidermal Junction

#### *Examining Structure and Function*

The DEJ has long been recognized as a structural anchoring membrane fixing basal keratinocytes to the dermal papillary layer. This structural adhesion aids in limiting shear forces from damaging the junction, distributing these shear forces among the undulating rete pegs seen with a healthy DEJ.<sup>5</sup> Flattening of the DEJ with aging, effacement of the structure weakens the adhesive forces, decreases the distribution of shearing forces, and subjects the skin to injury and damage, with a predisposition to tears.<sup>3</sup>

Less recognized in DEJ function are the specialized proteins that constitute the basement membrane, which are involved in signal transduction and communication between dermis and epidermis. These include laminins, collagens (IV), and integrins that regulate keratinocyte renewal through basal stem cell activity, fibroblast activity, and ECM remodeling.<sup>5,6</sup> Loss of DEJ integrity affects these functions with resultant degeneration in components of the skin.

Finally, the vascular component comprising the superficial vascular plexus lies in close proximity to the DEJ. With ECM degeneration and atrophy, and effacement of the DEJ with diminished rete pegs, vessel support is affected with increased fragility, resulting in the purpura and hemosiderin deposition seen in DP patients.<sup>2,3,7</sup>

## Clinical Evidence

In a multicenter randomized trial in 2024, Markowitz et al demonstrated that patients treated with an ECM modulating peptide formulation (ReFORM & RePAIR COMPLEX with TriHex Technology® (Alastin, a Galderma Company, Carlsbad)

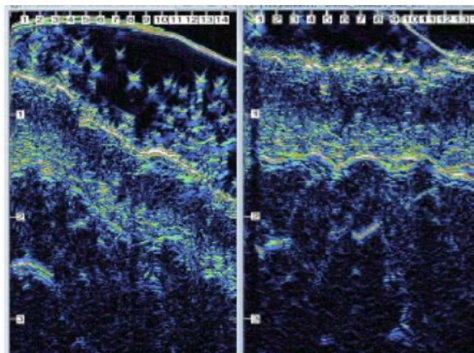
improved DEJ undulation in 83% of treated arms versus control. The R&R treatment arm demonstrated better transepidermal water loss (TEWL) recovery compared to the ceramide moisturizer treatment arm and resulted in increased skin resilience and less bruising and skin fragility than the comparator arms.<sup>4</sup> (Figure 1). Ultrasound evidence showed rete pegs re-establishment and thickening at 24 weeks (Figure 2), and the line-field confocal optical coherence tomography (LC-OCT) investigations confirmed the findings with increased density of DEJ obscuring the underlying vasculature<sup>4</sup> (Figures 3A, 3B).

Histology showed new collagen and elastin formation in the papillary dermis located adjacent to the DEJ, with marked regenerative activity evident in the area (as opposed to the comparator arms)<sup>14</sup> (Figure 4). It is noteworthy that these changes in the papillary dermis preceded new collagen and elastin formation in the deeper dermis, signaling that regeneration and reversal of DP is likely triggered and initiated at the DEJ.

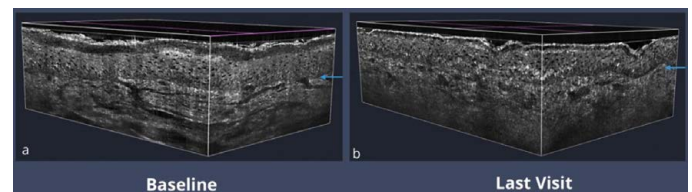
**FIGURE 1.** Patient treated with R&R showing typical result after 16 weeks of treatment demonstrating improved skin resilience, tightening and reduction of crepiness (baseline left, 16 weeks right).



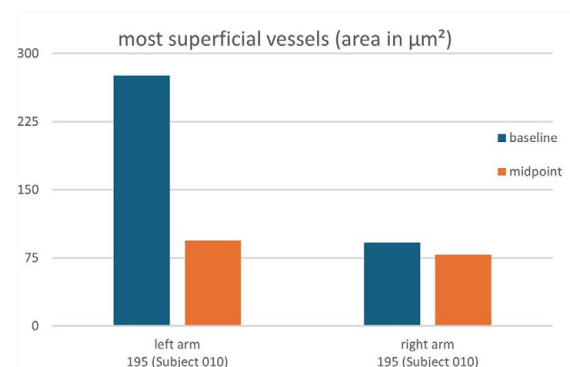
**FIGURE 2.** Ultrasound changes from baseline (left) to day 169 (right) highlighting reconstitution of basement membrane, DEJ, with improved demarcation between dermis and subcutaneous tissue



**FIGURE 3A.** LC-OCT also demonstrates reconstitution of basement membrane on side view – A 3D bloc view of the images shows this reconstitution and the improvement in DEJ (blue arrow) from a flattened indistinct DEJ with poor definition at Baseline (A) to a more undulated and well-defined DEJ (b) at the last visit

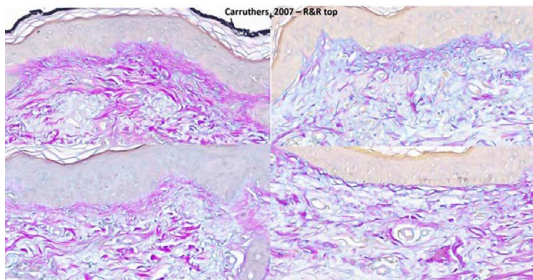


**FIGURE 3B.** Analysis of a typical case showing a marked decrease in vessel visibility in the left arm (R&R) after 6 weeks, compared to the right arm (bland moisturizer) which shows no such effect. This is a result of the re-establishment of the DEJ, obscuring the underlying vessels.

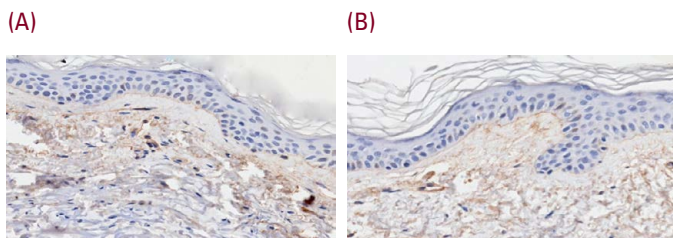


These changes are further validated through the histology analysis of Collagen IV and Laminin-5 (Figures 5 and 6). Representative 40x immunohistochemistry showing Collagen IV distribution at baseline (5A) pretreatment and (5B) posttreatment skin biopsies. Collagen IV staining appears as a linear band immediately beneath the basal keratinocyte layer. Following treatment, Collagen IV demonstrates a more organized and continuous staining profile, indicating remodeling of the basement membrane structure.

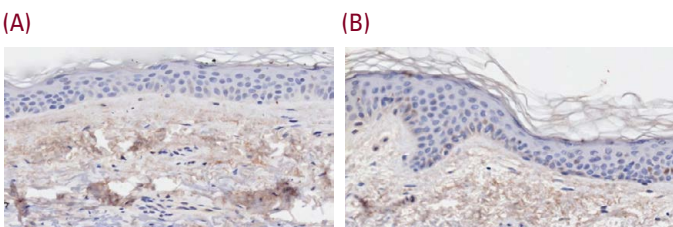
**FIGURE 4.** Herovici stain highlights increased new collagen fibers on the right side (Top) images as compared to the left (Top). More magenta to blue conversion top right (Top-R&R), denoting a change from mature collagen (magenta) to new fine fibers and mucopolysaccharides (blue) representing neocollagenesis. Also note new rete peg formation, reversal of effacement, all these changes in the top as opposed to the bottom pics representing the comparator moisturizer.



**FIGURE 5.** Immunohistochemistry staining of Collagen IV showing Baseline (pre-treatment) (A) and post-treatment (B). Baseline (A) shows a less continuous collagen IV staining with breaks in basement membrane continuity and lower intensity in places while post-treatment (B) displays a continuous and more organized along the entire DEJ.



**FIGURE 6.** Laminin-5 immunostaining at the dermal–epidermal junction before (A) and after (B) treatment, showing increased thickening, continuity and intensity of Laminin-5 along the DEJ post-treatment.



Immunohistochemistry (Figure 6) of Laminin-5 shows notable changes between pre (A) and posttreatment (B). At baseline (A), Laminin-5 staining appears relatively discontinuous and thinner in appearance along the DEJ. In contrast, posttreatment biopsies showed a more robust and continuous thickened staining of Laminin-5, demonstrating the signal intensity translating into a better DEJ architecture and integrity.

### Rationale

#### *Why Does the Process Start at the Dermoepidermal Junction?*

When one considers the histological and imaging changes that suggest initial changes in the DEJ heralding reversal of DP, a structural reconstitution would be a logical explanation. The ECM modulating peptide formulation restores basement membrane proteins with increased density, added rete peg depth, and resultant improved derm-epidermal adhesion. This manifests clinically as skin that is mechanically stable and firmer. Previous studies have shown increased CD-44 hyaluronic acid stimulation and growth factor signaling, such as HB-EGF (Heparin-Binding EGF-like Growth Factor), which stimulates keratinocyte proliferation and turnover, strengthens the basement membrane barrier, and improves skin resilience.<sup>3</sup> In addition to increased keratinocyte turnover, a healthy DEJ promotes keratinocyte-fibroblast crosstalk with integrin-mediated activation of fibroblasts and improves collagen and elastin formation. Finally, an improved sturdy basement membrane provides an ideal scaffold for superficial vasculature, strengthening vessels, reducing leakages, and decreasing purpura. This is supplemented by the later buildup of remodeled ECM that further provides support for these vessels.<sup>3</sup>

When one considers the DEJ-focused literature more broadly, independent studies also provide evidence for DEJ-initiated regeneration. Fisher et al demonstrated in healing wounds that basement membrane restoration preceded dermal and epidermal remodeling.<sup>8</sup> Shin et al stressed the importance of DEJ in maintaining dermal-epidermal integrity as an anti-aging strategy.<sup>9</sup> Iriyama et al demonstrated that regeneration of collagen in the papillary dermis was dependent on reconstruction of the basement membrane.<sup>10</sup> Rouselle et al showed that DEJ regeneration was important in keratinocyte polarity and basal stem cell activity<sup>6</sup> and Shen et al showed that loss of DEJ components with effacement of rete ridges affected mechanical strength and signaling across the barrier affecting skin aging.<sup>11</sup>

In summary, multiple studies have reinforced the concept that DEJ restoration not only manifests as a structural sign of repair, but functionally, this reconstitution appears to herald an overall regenerative milieu seen later in epidermal and dermal layers. The strategy of topical formulation targeting all these areas is logical, and the sequence of DEJ-initiated epidermal-dermal regeneration would appear to be sound.

## CONCLUSION

Dermatoporosis, although widespread among the population, is underrecognized. It is characterized by progressive thinning of all skin layers, leading to skin fragility and a lack of support for the vasculature, which results in leakage and purpura. Evidence gathered over the past few years now suggests that the reversal of this condition through a topical peptide-based formulation is initiated in the DEJ related to its early regeneration. This reconstitution provides structural anchoring, vascular support, followed by epidermal proliferation and increased activity (reversal of senescence) of dermal fibroblasts. Considering the DEJ as central and pivotal to DP reversal represents a new strategic paradigm to both mechanistic understanding and therapeutic approach.

## DISCLOSURES

Alan Widgerow is Chief Scientific Officer of Galderma. Faiza Shafiq is Director of Clinical Research, Alastin, a Galderma Company. Faiza Shafiq is also full-time employee at Galderma (Director of Clinical Studies). The other authors have no conflicts of interest to disclose.

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## AUTHOR CORRESPONDENCE

**Alan D. Widgerow MBBCh MMed FCS FACS**

E-mail:..... alan.widgerow@galderma.com

# Rapid Clearance of Lichen Planus With Topical Tapinarof

Olivia R. Noble BS, Evelina N. Pierce MD

Skin Cancer Specialists, P.C., Dallas, GA

## ABSTRACT

**Background:** Lichen planus (LP) is an auto-inflammatory idiopathic condition affecting skin, mucous membranes, hair follicles, and nails that presents as pruritic, violaceous papules and plaques. No FDA-approved treatments exist for LP.

**Case Presentation:** A 70-year-old female presented with scalp pruritus and pruritic eruption on bilateral shins. She was treated for presumed seborrheic and contact dermatitis; however, after 2 months, she had no improvement. On biopsy, scalp and right shin samples were consistent with lichen planopilaris and LP, respectively. The patient was treated with hydroxychloroquine, pimecrolimus, fluocinonide, and tofacitinib 2% creams, and intralesional Kenalog. Four months later, she had complete resolution of the scalp rash, but the rash on the shins persisted. We discontinued tofacitinib, fluocinonide, and pimecrolimus and prescribed tapinarof 1% cream once daily. After 1 month, her scalp condition remained in remission, and the LP on the shins completely resolved with minimal post-inflammatory hyperpigmentation.

**Conclusion:** To our knowledge, this is the first report in the literature showing successful treatment of LP with tapinarof. Further studies are required to determine if tapinarof is beneficial for the treatment of lichenoid diseases such as LP, lichen planopilaris, and others.

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## INTRODUCTION

Lichen Planus (LP) is an auto-inflammatory idiopathic condition with unclear etiology, believed to be an auto-reactive response of T-cell-mediated damage after exposure to an inciting antigen. LP presents as pruritic, violaceous papules and plaques most commonly on the volar wrists, flexural surfaces, and trunk. Histologically, LP is characterized by a band-like lichenoid lymphocytic infiltrate with vacuolar destruction of the basal layer.<sup>1</sup> LP has no FDA-approved treatments. Typical off-label treatments are topical and systemic steroids, anti-malarials, retinoids, antibiotics, immunosuppressants, phototherapy, and recently, apremilast and oral and topical Janus kinase inhibitors.<sup>1,2</sup> We present the case of a 70-year-old female with a history of LP and lichen planopilaris who experienced complete resolution of LP after using tapinarof 1% topical cream.

### Case Presentation

A 70-year-old female presented to the clinic with complaints of scalp pruritus and pruritic eruption on bilateral shins lasting several weeks. Her medical history was significant for acid reflux, for which she was taking famotidine.

On examination, we observed erythema and subtle perifollicular scaling at the scalp, as well as erythematous and cobble-stoning flat-topped papules coalescing into plaques on the bilateral shins. She was treated for presumed seborrheic dermatitis with ketoconazole shampoo and clobetasol solution. Fluocinonide cream was prescribed for the shins.

**FIGURE 1.** Initial presentation with erythematous and cobble-stoning flat-topped papules coalescing into plaques extended over the shin.



She returned after 2 months, reporting no improvement in either condition. Two biopsies were performed. The biopsy of the right temporal scalp showed hyperkeratosis of the epidermis and fibrosis with chronic inflammation centered around the hair follicles in the dermis. The biopsy of the right shin showed hyperkeratosis and hypergranulosis with a band-like lymphocytic infiltrate. These findings were consistent with lichen planopilaris and LP, respectively.

The patient was started on hydroxychloroquine 200 mg twice daily. Hepatitis C was negative. CBC and CMP were unremarkable. She denied mucus membrane or nail involvement. The scalp was treated with intralesional Kenalog 2.5 mg/mL. Pimecrolimus and compounded tofacitinib 2% creams were added.

**FIGURE 2.** Scalp biopsy site of erythema and subtle perifollicular scaling.



**FIGURE 3.** Erythematous plaques and cobble-stoning flat-topped papules on the shin at the time of the skin biopsy.



The patient returned 4-months later with complete resolution of the scalp rash; however, the rash on the shins persisted. We discontinued tofacitinib, fluocinonide, and pimecrolimus. She was given tapinarof 1% cream to use once daily. She returned 1 month later with complete resolution of her LP on the shins with minimal post-inflammatory hyperpigmentation. The scalp continued in remission without any topical treatments.

## DISCUSSION

LP is a prototypical disorder of lichenoid dermatoses, such as lichen planopilaris, pityriasis lichenoides, lichen striatus, etc. It is an auto-reactive condition, believed to result from CD8+ cytotoxic T-cell-mediated reactions against basal keratinocytes, further influenced by T helper (Th) pathways, such as Th1 and Th17/interleukin (IL)-23 axis.<sup>3</sup> LP is thought to be a response to foreign antigens such as infections (hepatitis C, human herpesviruses, COVID-19), vaccinations, contact allergens (dental metals), and medications (ACE-inhibitors, beta blockers).<sup>1,3,4</sup> LP is classically described as purple, planar, pruritic papules and plaques with Wickham striae in some lesions.

Several alterations in the expression of cytokines and chemokines in lesions or serum of patients with LP have been described. Serum concentrations of IL-5, IL-6, IL-8, IL-9, IL-10, IL-12, IL-17, IL-22, TNF- $\alpha$ , transforming growth factor- $\beta$ , and interferon (IFN)- $\gamma$  have been found to be elevated.<sup>1</sup> Increased expression

**FIGURE 4.** Interim clearance of lichen planus on regimen daily tapinarof 1% cream over a 1-month period.



of IFN- $\gamma$  and IL-17 in LP lesions has also been described.<sup>1</sup> The lesions also have an increased number of mast cells, indicating that non-specific mechanisms such as mast cell degranulation and protease activation are involved in LP pathogenesis. These mechanisms may combine to cause T-cell accumulation and induce keratinocyte apoptosis.<sup>1</sup>

In addition, analysis of the relationship between nitrosative stress, antioxidant defense, and inflammation offers insights into the role of the nitric oxide pathway in LP pathogenesis. Increased concentrations of nitrosative stress markers, such as nitrates and nitrites, in patients with LP were positively correlated with concentrations of C-reactive protein and negatively correlated with markers of total antioxidant status, indicative of pro-inflammatory status and impaired antioxidant defense in LP.<sup>5</sup>

Most off-label treatments used for LP give inconsistent results. We found the use of tapinarof 1% cream led to rapid and complete clearance of LP. Tapinarof is a small-molecule therapeutic agent that uniquely activates the aryl hydrocarbon receptor (AhR) pathway to decrease oxidative stress, re-establish skin homeostasis, and decrease multiple pro-inflammatory cytokines, including several cytokines relevant in LP pathogenesis (IL-17, IL-22, IFN- $\gamma$ , IL-5, IL-6, IL-8).<sup>6,7</sup>

AhR is a transcription factor ubiquitously expressed by epithelial and immune cell types,<sup>8</sup> including keratinocytes, antigen-presenting cells, Langerhans cells, mast cells, T and B cells.<sup>7,9</sup> AhR is believed to increase antioxidant activity via the nuclear factor erythroid 2-related factor 2 pathways, thereby decreasing oxidative stress in the skin.<sup>9</sup> AhR exerts numerous effects on mast cells, B cells, macrophages, antigen-presenting cells, Th1/Th2 cell balance, Th17 cells, and regulatory T cells.<sup>10</sup> Notably, Th17 cells express AhR at high concentrations. AhR downregulates Th17 cell differentiation as well as IL-17 and IL-22 production.<sup>6</sup> AhR also suppresses Th2 cell differentiation and the production of IL-4, IL-5, IL-13, and IL-31 cytokines.<sup>7,8</sup> AhR regulates inflammatory signals via crosstalk with other signaling pathways, such as the nuclear factor kappa B pathway,<sup>6,7</sup> which

controls the expressions of IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ , and other inflammatory genes.<sup>6</sup> Given involved cytokine pathways, AhR may be implicated in the modulation of the normal differentiation of Th1/Th2 cells, which explains tapinarof's efficacy in atopic dermatitis, psoriasis, and, in this case, LP. More studies are needed to evaluate tapinarof's efficacy for lichenoid dermatoses such as LP.

## CONCLUSION

Our patient experienced complete remission of LP within one month of initiating treatment with topical tapinarof. To our knowledge, this is the first case report in the literature showing successful treatment of LP with tapinarof. The unique mechanism of action of tapinarof, its modulation of cytokine pathways and oxidative stress reduction, may explain its effectiveness in Th1 and Th2 predominant conditions, such as atopic dermatitis, psoriasis, and, in this case, LP.

This case report highlights the potential role tapinarof may play in the treatment of LP and other lichenoid diseases, such as lichen planopilaris, pityriasis lichenoides chronica, etc.

## DISCLOSURES

A medical writing assistance grant was provided by Organon. Authors do not have any other conflicts of interest to disclose.

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## AUTHOR CORRESPONDENCE

**Olivia R. Noble BS**

E-mail:..... oliviarnoble@yahoo.com

# Successful Treatment of Dystrophic Epidermolysis Bullosa With the JAK1 Inhibitor Abrocitinib

Fang Wang MM,<sup>a-d</sup> Ranran Zhang MM,<sup>a-d</sup> Ying Fang MM,<sup>a-d</sup> Shan Zhou MM,<sup>a-d</sup> Jiaming Dong MM,<sup>a-d</sup> Tingting Han MM,<sup>a-d</sup> Qiaoyue Tang MM,<sup>a-d</sup> Yixiao Wang MM,<sup>a-d</sup> Zhenyu Zhong MM,<sup>e</sup> Min Gao MD<sup>a-d</sup>

<sup>a</sup>Department of Dermatology, The First Affiliated Hospital, Anhui Medical University, Hefei, 230032 Anhui, China

<sup>b</sup>Institute of Dermatology, Anhui Medical University, Hefei, 230032 Anhui, China

<sup>c</sup>Key Laboratory of Dermatology (Anhui Medical University), Ministry of Education, Hefei, 230032 Anhui, China

<sup>d</sup>Collaborative Innovation Center of Complex and Severe Skin Disease, Anhui Medical University, Hefei, 230032 Anhui, China

## ABSTRACT

**Introduction:** JAK inhibitors are increasingly being utilized for the treatment of diseases beyond their nonclassical indications, and the highly selective JAK1 inhibitor abrocitinib may represent a promising therapeutic option for dystrophic epidermolysis bullosa (DEB).

**Case Presentation:** The first case was a 39-year-old male with DEB in whom conventional therapy was ineffective. After one month of abrocitinib treatment, marked improvement in both pruritus and skin lesions was observed, with no adverse drug reactions during six months of therapy. The second case involved a 46-year-old female DEB patient in whom conventional therapy resulted in mild improvement of skin lesions but no significant relief of pruritus.

**Conclusion:** The present two cases provide comparative evidence suggesting the superior efficacy of abrocitinib relative to conventional therapies for DEB.

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## INTRODUCTION

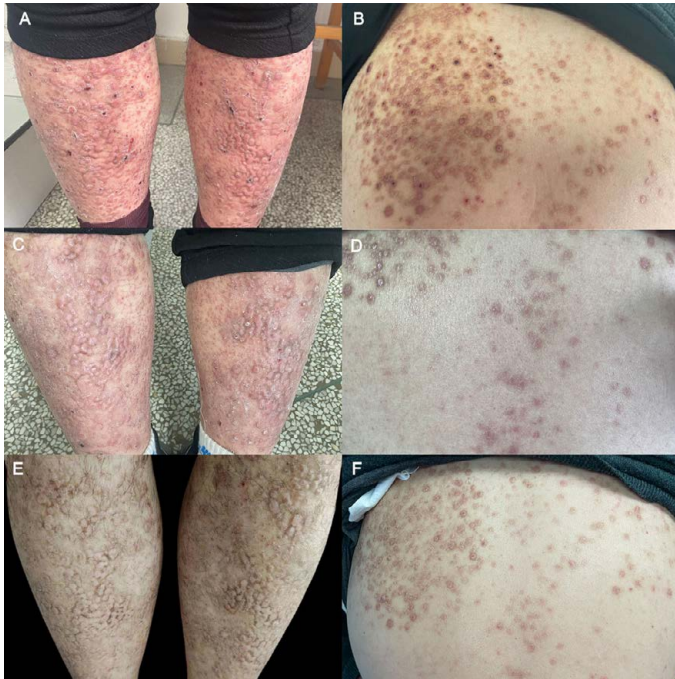
Dystrophic epidermolysis bullosa (DEB), caused by mutations in *COL7A1* is characterized by the development of blisters, bullae, and erosions following minor trauma to the skin and mucous membranes, with healing typically resulting in atrophic scarring and associated nail dystrophy.<sup>1,2</sup> However, no cure for DEB is available; therefore, the clinical care and quality of life of patients need considerable improvement. Currently, JAK inhibitors are being increasingly utilized in the management of noncanonical indications, demonstrating promising clinical efficacy across diverse disease contexts. Here, we report that JAK1 inhibitor abrocitinib may be an effective therapeutic strategy for DEB, supported by case evidence.

## CASE PRESENTATION

The first case was a 39-year-old male proband with DEB who initially presented with localized erythema and blisters during adolescence. Subsequently, the rash spread to the trunk and extremities with obvious itching. The proband's mother, grandmother, and aunt manifested similar clinical manifestations. Clinical examination revealed diffuse erythema with papules and nodules distributed across the trunk and extremities, accompanied by scattered hemorrhagic crusts,

scales, and hypertrophic scar tissue formation (Figure 1A, B). Genetic testing of the proband and his mother revealed a heterozygous missense variant in *COL7A1*: c.5099G>T (p.Gly1700Val). The patient had previously undergone treatment with oral antihistamines (eg, ebastine, cetirizine, and loratadine), corticosteroids, and cyclosporine, yet the clinical efficacy was unsatisfactory. Due to significant pruritus, the patient was initiated on oral abrocitinib (Pfizer, New York, USA) at a dosage of 100 mg daily. One week later, the symptoms exhibited no significant improvement. Based on prescribing recommendations, the dosage of abrocitinib was increased to 200 mg orally per day. After only one month of treatment, a significant reduction in pruritus and inflammation was observed; the rash improved, and blood crusts sloughed off (Figure 1C, D). The Visual Analog Scale score for pruritus decreased from 8 to 1. The patient reported significant improvements in pruritus and sleep quality. After 3 months, complete resolution of diffuse erythema was achieved with flattening of the rash, although some dark-brown hyperpigmentation and scars remained (Figure 1E, F). During the six-month follow-up period, routine examinations of blood and urine, liver and kidney function, electrolytes, and coagulation parameters were performed periodically, with no abnormalities detected and no adverse drug reactions reported.

**FIGURE 1.** Clinical course in Case 1 during abrocitinib treatment. The patient at the baseline (A, B), after treatment for 1 month (C, D), and 3 months (E, F).



In the second case, a 46-year-old female with DEB had blisters on her right ankle at birth that recurred over many years, accompanied by ulceration, crusting, and oral mucosal involvement. Progressive dysphagia emerged later in her clinical trajectory. The patient had a family history. Clinical examination revealed large, broken red vesicular areas on the head and neck, trunk, and extremities; some were dry and crusted; extensive tooth loss with dental caries; and contracture deformity of the fingers of both hands (Figure 2A-D). Genetic testing revealed one pathogenic variant, c.6187C>T (p.Arg2063Trp), and one suspected pathogenic variant, c.4965C>T (p.(Gly1655=)) in the *COL7A1* gene. The patient exhibited prominent symptoms, including intense pruritus, for which the administration of abrocitinib was recommended as a therapeutic intervention. The patient declined this treatment option due to financial considerations, and was treated with loratadine, ebastine, sulperazone, aggressive debridement and dressing changes, red and blue light irradiation, albumin, and blood transfusion support. The patient exhibited mild regression of cutaneous lesions; however, pruritus remained persistent.

## DISCUSSION

Refractory itching is the most distressing disease-related symptom in patients with DEB, resulting in an itch-scratch-blister cycle.<sup>3</sup> Research has shown that patients with DEB exhibit

**FIGURE 2.** Clinical appearance in Case 2. (A-D) shows widespread skin peeling, blisters, erosions, crusting, with caries and finger deformities throughout the patient.



immune dysregulation affecting both the skin and systemic levels, characterized by increased production of inflammatory cytokines, including IL-1 $\beta$ , IL-2, IL-6, IL-10, interferon- $\gamma$ , and TNF- $\alpha$ .<sup>4</sup> The JAK-STAT signaling pathway is involved in the signal transduction of multiple cytokines and their receptors, playing a broad role in various biological processes, including immune regulation, inflammatory responses, cell proliferation, and differentiation.<sup>5</sup> Therefore, targeting the JAK-STAT pathway may be a promising approach for the treatment of patients with DEB. In addition to atopic dermatitis, abrocitinib, a highly selective JAK1 inhibitor, has been shown to be effective in dozens of other inflammatory diseases, such as lichen sclerosus, alopecia areata, prurigo nodularis, and hidradenitis suppurativa.<sup>6</sup>

Recent studies have underscored the significant efficacy of JAK inhibitors in alleviating pruritus associated with DEB. To date, a total of 30 DEB patients, aged 12 to 71 years, have received JAK inhibitor therapy, including 2 treated with tofacitinib, 7 with baricitinib, 15 with upadacitinib, and 6 with abrocitinib.<sup>7-17</sup> The majority of these patients exhibited substantial clinical improvement in both cutaneous lesions and pruritus, with only one patient displaying a lack of therapeutic response. Regarding safety, no serious adverse reactions were reported in any of the patients. Therefore, the treatment of a DEB patient without atopic dermatitis using 200 mg of abrocitinib was effective, affirming the drug's effectiveness and feasibility as a therapeutic option. However, the study's limitations include a small sample size and the absence of a comparator treatment group.

## CONCLUSION

DEB is a persistent, relapsing disease that severely affects the quality of life. The findings of this study suggest that abrocitinib may represent a viable therapeutic option for DEB, demonstrating pronounced efficacy in pruritus relief compared

to conventional treatments. However, larger-scale studies are warranted to fully elucidate the efficacy and safety profile of JAK inhibitors in DEB.

## DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## AUTHOR CORRESPONDENCE

Min Gao MD

E-mail:..... ahnngm@126.com

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# Association Between Topical Ruxolitinib Treatment and Psychiatric Outcomes in Adults With Vitiligo

Kermanjot Sidhu BS,<sup>a</sup> Kritin Verma MBA,<sup>b</sup> Sahil Kapur BS,<sup>c</sup> Kevin Nguyen BA,<sup>b</sup> Iltefat Hamzavi MD,<sup>d</sup> Henry Lim MD,<sup>d</sup> Karan Pandher MD<sup>c</sup>

<sup>a</sup>Michigan State University College of Human Medicine, Grand Rapids, MI

<sup>b</sup>Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX

<sup>c</sup>University of Toledo College of Medicine and Life Sciences, Toledo, OH

<sup>d</sup>Center for Cutaneous Biology and Immunology Research, Department of Dermatology, Henry Ford Health, Detroit, MI

<sup>e</sup>Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

## INTRODUCTION

Vitiligo is a chronic autoimmune skin disorder characterized by progressive loss of epidermal melanocytes, resulting in depigmented macules and patches.<sup>1</sup> The visible nature of vitiligo can impose a substantial psychosocial burden, including diminished quality of life, reduced self-esteem, and impaired social functioning.<sup>2,3</sup> Psychiatric comorbidities, particularly depression and anxiety, occur at disproportionately high rates in this population and are frequently attributed to the visible and often stigmatizing nature of the disease.<sup>4</sup> Lesions commonly appear on cosmetically sensitive and visible areas, such as the face and hands, amplifying social scrutiny and emotional distress.<sup>3,5</sup>

Recent therapeutic advances have introduced topical Janus kinase (JAK) inhibitors, including ruxolitinib 1.5% cream, as targeted treatments for repigmentation in vitiligo.<sup>6</sup> Ruxolitinib inhibits JAK1 and JAK2 signaling pathways implicated in autoimmune melanocyte destruction, and phase three clinical trials have demonstrated meaningful clinical repigmentation with favorable tolerability profiles.<sup>6,7</sup> Despite the recognized psychiatric burden of vitiligo, limited evidence exists regarding whether effective treatments such as topical ruxolitinib confer measurable benefits in reducing incident psychiatric comorbidities. The present study leverages large-scale, real-world data to examine the association between topical ruxolitinib use and psychiatric disorders among adults with vitiligo.

## MATERIALS AND METHODS

We performed a retrospective, propensity score-matched cohort analysis on TriNetX comparing adult patients with vitiligo treated with topical ruxolitinib to matched controls without ruxolitinib exposure. Adults with vitiligo were identified using the International Classification of Diseases (ICD-10) code L80 and matched 1:1 on age, sex, race, and ethnicity, resulting in two balanced cohorts of 4,936 patients each. Treatment status was determined from prescription records for ruxolitinib (RxNorm 1193326). Since no code distinguishes topical from oral

formulations, prescriptions were restricted to those originating in dermatologic outpatient settings, and patients with hematologic or myeloproliferative diseases, typically treated with oral ruxolitinib (ICD-10 D47.4, D45, D89.810, D89.813, D76.1, D47.1, C94.3) were excluded.

Psychiatric and behavioral outcomes were identified using valid ICD-10 codes, while procedural and mental health service utilization outcomes were captured via Current Procedural Terminology (CPT) codes. Incidence rates were compared between groups using relative risk (RRs) with 95% confidence intervals (CIs) calculated using Wald's method. Statistical significance was determined by two-tailed *P*-values, with significance defined as *P* < 0.05. The observation period for outcomes started one day after the index date, which was defined as the first topical ruxolitinib prescription date for treated patients or a matched index date for controls, and extended through available follow-up.

## RESULTS

Patients treated with topical ruxolitinib exhibited significantly lower rates of multiple psychiatric comorbidities and mental health service utilization compared to untreated controls (Table 1). Depressive episodes occurred in 1.9% of the treated group versus 7.2% in controls (RR 0.26; CI 0.21–0.33). Recurrent major depressive disorder was similarly reduced (0.9% vs 3.3%; RR 0.27; CI 0.19–0.37). Significant risk reductions were also observed for phobic anxiety disorders (RR 0.43; CI 0.24–0.79), other anxiety disorders (RR 0.33; CI 0.28–0.39), persistent mood disorders (RR 0.297; CI 0.16–0.54), and unspecified mood disorders (RR 0.37; CI 0.22–0.62). Sleep disorders unrelated to substances or known physiological conditions were also reduced (0.73% vs 2.67%; RR 0.28; CI 0.19–0.40). Additionally, mental and behavioral disorders due to psychoactive substance use were less common in treated patients (1.09% vs 4.80%; RR 0.22; CI 0.17–0.30).

The association with obsessive-compulsive disorder did not achieve statistical significance (RR 0.53; CI 0.25–1.13). Although the point estimates for bipolar disorder (RR 0.23; CI 0.12–0.46)

TABLE 1.

| Relative Risk of Psychiatric Comorbidities in Adults With Vitiligo Treated With Topical Ruxolitinib 1.5% Cream versus Without |                                                                              |       |                                                                                   |        |                        |          |
|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------|--------|------------------------|----------|
| Outcomes                                                                                                                      | Vitiligo Patients Treated with Topical Ruxolitinib ≥18 Years Old (n = 4,936) | %     | Vitiligo Patients without Topical Ruxolitinib Treatment ≥18 Years Old (n = 4,936) | %      | Relative Risk (95% CI) | P-value  |
| Depressive episode                                                                                                            | 94                                                                           | 1.90% | 355                                                                               | 7.19%  | 0.26 (0.21,0.33)       | < 0.0001 |
| Major depressive disorder, recurrent                                                                                          | 43                                                                           | 0.87% | 163                                                                               | 3.30%  | 0.27 (0.19,0.37)       | < 0.0001 |
| Phobic anxiety disorders                                                                                                      | 15                                                                           | 0.30% | 35                                                                                | 0.71%  | 0.43 (0.24,0.79)       | 0.0049   |
| Other anxiety disorders                                                                                                       | 152                                                                          | 3.08% | 478                                                                               | 9.68%  | 0.33 (0.28,0.39)       | < 0.0001 |
| Persistent mood disorders                                                                                                     | 14                                                                           | 0.28% | 47                                                                                | 0.95%  | 0.30 (0.16,0.54)       | < 0.0001 |
| Unspecified mood disorder                                                                                                     | 20                                                                           | 0.41% | 54                                                                                | 1.09%  | 0.37 (0.22,0.62)       | < 0.0001 |
| Sleep disorders not due to a substance or known physiological condition                                                       | 36                                                                           | 0.73% | 132                                                                               | 2.67%  | 0.28 (0.19,0.40)       | < 0.0001 |
| Mental and behavioral disorders due to psychoactive substance use                                                             | 54                                                                           | 1.09% | 237                                                                               | 4.80%  | 0.22 (0.17,0.30)       | < 0.0001 |
| Obsessive-compulsive disorder                                                                                                 | ≤ 10*                                                                        | -     | 19                                                                                | 0.38%  | 0.53 (0.25,1.13)       | 0.0952   |
| Bipolar disorder                                                                                                              | ≤ 10*                                                                        | -     | 43                                                                                | 0.87%  | 0.231 (0.12,0.46)      | < 0.0001 |
| Schizophrenia, schizotypal and delusional disorders                                                                           | ≤ 10*                                                                        | -     | 37                                                                                | 0.75%  | 0.269 (0.13,0.54)      | < 0.0001 |
| Outpatient Visits                                                                                                             | 107                                                                          | 2.17% | 563                                                                               | 11.41% | 0.32 (0.27,0.39)       | < 0.0001 |
| Psychiatry Services and Procedures                                                                                            | 45                                                                           | 0.91% | 149                                                                               | 3.02%  | 0.31 (0.22,0.43)       | < 0.0001 |

\* Indicates outcomes with ≤10 patients; effect estimates for these outcomes should be interpreted with caution due to limited sample size or data availability.

and schizophrenia, schizotypal, and delusional disorders (RR 0.27; CI 0.13–0.54) suggested a reduced risk in treated patients, the small number of events limited the precision of these findings and should be interpreted with caution due to limited statistical power. Mental health service utilization was significantly reduced in treated patients, with outpatient psychiatric visits occurring in 2.17% versus 11.41% of treated versus untreated patients (RR 0.32; CI 0.27–0.39), and overall psychiatric services utilization similarly reduced (0.91% vs 3.02%; RR 0.31; CI 0.22–0.43).

DISCUSSION

Our large, multicenter analysis demonstrates that adults with vitiligo who were prescribed topical ruxolitinib exhibited markedly lower incidence of several psychiatric comorbidities compared with matched patients unexposed to the drug. Specifically, significant reductions in depressive episodes,

recurrent major depressive disorder, multiple anxiety disorders, persistent mood disorders, substance use disorders, and sleep disturbances were identified. These findings extend beyond the established cutaneous efficacy of topical ruxolitinib by suggesting potential secondary mental health benefits associated with its use in vitiligo populations.

These findings raise the possibility that effective repigmentation treatment with topical ruxolitinib may mitigate psychiatric morbidity by alleviating psychosocial distress, restoring skin appearance, and modifying patient self-perception. While the psychiatric benefit is plausibly mediated by visible repigmentation and improved quality of life, the biological mechanism underlying these associations warrants further exploration.<sup>8</sup> Cytokines regulated through JAK signaling, including interleukins (eg, IL-1β, IL-6) and interferons (eg, IFN-γ), have been implicated in the pathogenesis of depression and

anxiety via neuroinflammatory activation of the JAK–signal transducer and activator of transcription (STAT) pathway.<sup>9-11</sup> Thus, ruxolitinib's effects may not only be symptomatic through cutaneous improvements but may also reflect systemic modulation of inflammatory signals relevant to neuropsychiatric health.<sup>12</sup> Unraveling these mechanisms is a key avenue for future mechanistic and translational studies.

Despite these encouraging results, several considerations temper interpretation. First, the study design was retrospective and relied on administrative coding, which introduces inherent susceptibility to misclassification bias. Although ICD-10 and CPT code algorithms provide validated means for identifying outcomes, they cannot fully capture psychiatric symptom severity, subclinical distress, or patient-reported quality of life, which are often the most relevant outcomes to patients. Additionally, reliance on prescription records to classify exposure could not conclusively differentiate topical from oral ruxolitinib, and our exclusion of patients with hematologic disorders cannot fully eliminate potential misclassification. These limitations underscore the need for confirmatory studies with verified treatment exposure.

Furthermore, the observed psychiatric benefits may be confounded by healthcare utilization patterns. Patients prescribed novel, specialty dermatologic treatments may have greater healthcare access, closer physician follow-up, and enhanced psychosocial support compared to untreated patients. These factors could independently reduce psychiatric morbidity. Although propensity score matching balanced demographic variables, residual confounding by socioeconomic status, disease severity, and location, or access to mental health services cannot be excluded.

While the temporal design ensured that outcomes were assessed after treatment initiation, retrospective observational analyses cannot definitively exclude reverse causation or unmeasured confounding. Randomized controlled trials incorporating psychiatric endpoints or large-scale prospective registries would be necessary to establish causality. Finally, although our study suggests a link between topical ruxolitinib use and improved psychiatric outcomes, whether these benefits are attributable to the drug itself, the process of treatment engagement, or the downstream psychosocial impact of visible repigmentation remains unresolved. Integrating objective skin-related outcomes (eg, Vitiligo Area Scoring Index (VASI), Patient Global Impression (PGI) scale) with validated psychiatric assessment tools could clarify the mediating pathways in future research.

## CONCLUSION

Topical ruxolitinib use in adults with vitiligo was associated with a significantly reduced risk of developing diverse psychiatric disorders, reflecting benefits that extend beyond its

cutaneous effects. These novel findings highlight the complex and bidirectional relationship between dermatologic disease activity and psychosocial health, emphasizing the importance of treatments that address both the visible manifestations of vitiligo and its often profound emotional and mental health impacts.

## DISCLOSURES

Iltefat Hamzavi has served as an advisory board member for AbbVie; a consultant for Boehringer Ingelheim, AVITA Medical, Galderma Laboratories LP, Incyte, Pfizer, and UCB; a principal investigator for AVITA, Bayer, Estee Lauder, Ferndale Laboratories, Incyte Corporation, Lenicura, L'Oreal, Pfizer, and Unigen; immediate past president of the HS Foundation; and a board member of the Global Vitiligo Foundation. Henry Lim reports receiving investigator/research grants to his institution from Incyte, L'Oreal, Pfizer, and PCORI, acting as a consultant for ISDIN, Beiersdorf, Ferndale, L'Oréal, Eli Lilly, Zerigo Health, Skinosive, Kenvue, NAOS, and Cantabria Labs, and as a speaker at general educational sessions for La Roche-Posay, Cantabria Labs, Pierre Fabre, NAOS, Uriage, Pfizer, and ISDIN. All other authors have no financial disclosures or conflicts of interest.

IRB approval: This study was considered by our IRB to be non-human research and thus exempt from review.

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## AUTHOR CORRESPONDENCE

Kermanjot S. Sidhu BS

E-mail:..... sidhuker@msu.edu

# Delays in Medical Care Among Skin of Color Melanoma Patients: A Population-Based Study

Sabrina Khan MD,<sup>a\*</sup> Charlotte Jeong BS,<sup>b\*</sup> Caterina Zagona-Prizio MD,<sup>c</sup> Manan D. Mehta MD,<sup>d</sup> Nicole Maynard MD,<sup>e</sup> Rasika Reddy MD,<sup>f</sup> Danielle Yee MD,<sup>g</sup> April W. Armstrong MD MPH<sup>a</sup>

<sup>a</sup>Division of Dermatology, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA

<sup>b</sup>University of Arkansas for Medical Sciences College of Medicine, Little Rock, AR

<sup>c</sup>Department of Dermatology, University of Colorado School of Medicine, Boulder, CO

<sup>d</sup>Department of Dermatology, State University of New York (SUNY) Downstate Health Sciences University, Brooklyn, NY

<sup>e</sup>Department of Psychiatry and Human Behavior, University of California, Irvine, School of Medicine, Irvine, CA

<sup>f</sup>Department of Dermatology, University of Southern California Keck School of Medicine, Los Angeles, CA

<sup>g</sup>Department of Dermatology, University of California Davis School of Medicine, Sacramento, CA

\*Co-first authors

## INTRODUCTION

In the United States (US), the incidence of melanoma, the most aggressive and fatal type of skin cancer, has been increasing at an average rate of 1.4% annually over the last decade.<sup>1</sup> Individuals with skin of color (SOC) have a markedly lower incidence of melanoma compared to their white counterparts.<sup>1</sup> However, SOC patients suffer from worse clinical outcomes, including diagnosis at more advanced stages<sup>2</sup> and consequently, lower rates of survival.<sup>3-5</sup> SOC patients consistently present with later stages of melanoma, regardless of the location of the lesion.<sup>5</sup> Barriers to obtaining medical care may contribute to challenges in early detection and appropriate management of melanoma. It is critical to investigate the determinants of timely access to healthcare to address gaps in diagnosis and treatment. This study aims to compare delays in access to medical care between SOC and white melanoma patients in the US and to characterize reasons for delayed care.

## MATERIALS AND METHODS

We conducted a nationally representative, cross-sectional study utilizing the National Health Interview Survey from 2007–2018 in respondents with a self-reported history of melanoma skin cancer. Respondents were identified as SOC if they identified as Black, Asian, American Indian/Alaskan Native, or Native Hawaiian/Pacific Islander. Respondents were asked if they received delayed medical care in the past 12 months for the following reasons: 1) inability to obtain an appointment, 2) clinic not open, 3) unable to reach a physician/clinic by telephone, 4) lacked transportation, 5) wait was too long to see a physician. Multivariable logistic regression was used to model the odds of receiving delayed care. Analyses were performed using the svy suite of commands in Stata 15.0. Threshold for significance was set at  $P < 0.05$ .

## RESULTS

Among the 8,904,798 weighted respondents with melanoma, 266,641 (3.1%) self-identified as SOC (Table 1). Compared to white patients, a significantly greater percentage of SOC patients reported receiving delayed medical care due to inability to obtain appointment (18.9% vs 8.3%,  $P = 0.0048$ ), inability to reach the physician/clinic by phone (12.4% vs 2.7%,  $P = 0.0001$ ), lack of transportation (9.6% vs 1.6%,  $P = 0.0001$ ), and long wait time (10.3% vs 3.9%,  $P = 0.0341$ ; Table 1). SOC patients with melanoma were 2.27 times more likely to receive delayed access to medical care compared to white patients when controlling for age, sex, insurance status, income, education level, and region (aOR [95% CI] = 2.27 [1.01–5.10]; Table 2).

## DISCUSSION

Overall, our findings suggest that SOC individuals with melanoma have higher odds of obtaining delayed medical care compared to white melanoma patients. Delays in access to necessary healthcare services can exacerbate or partially explain previously established racial disparities in the detection, management, and survival of melanoma.<sup>4</sup> Specifically, barriers in access may further prolong presentation and diagnosis at later stages. Furthermore, difficulty obtaining appropriate medical services can worsen delays in treatment; non-white patients have been shown to experience delays in surgical excision of melanoma compared to white patients.<sup>6</sup> These factors may contribute to the lower melanoma-specific survival seen in SOC patients.<sup>3</sup>

Moreover, our study identified the inability to obtain an appointment (18.9%) and the inability to reach a clinic by telephone (12.4%) as common causes of receiving delayed care among SOC melanoma patients. Given that SOC patients

TABLE 1.

| Demographic Characteristics and Reasons for Receiving Delayed Medical Care in Skin of Color Melanoma Patients vs White Melanoma Patients from 2007–2018 |                                                |                                          |                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------|---------------------|
| Characteristic                                                                                                                                          | Skin of Color Melanoma Patients<br>(n=266,641) | White Melanoma Patients<br>(n=8,638,157) | P-Value             |
| Age (mean, y)                                                                                                                                           | 62.4                                           | 64.5                                     | 0.221 <sup>a</sup>  |
| Sex, n (%)                                                                                                                                              |                                                |                                          |                     |
| Male                                                                                                                                                    | 162,868 (61.1%)                                | 4,188,161 (48.5%)                        | 0.046 <sup>b</sup>  |
| Female                                                                                                                                                  | 103,773 (38.9%)                                | 4,449,996 (51.5%)                        |                     |
| Annual Household Income, n (%)                                                                                                                          |                                                |                                          |                     |
| \$0-\$49,999                                                                                                                                            | 134,028 (54.2%)                                | 3,570,515 (44.9%)                        | 0.292 <sup>b</sup>  |
| \$50,000-\$99,999                                                                                                                                       | 73,710 (29.8%)                                 | 2,429,450 (30.6%)                        |                     |
| >\$100,00                                                                                                                                               | 39,449 (16.0%)                                 | 1,946,922 (24.5%)                        |                     |
| Education, n (%)                                                                                                                                        |                                                |                                          |                     |
| < HS graduate                                                                                                                                           | 50,018 (28.7%)                                 | 711,123 (13.4%)                          | 0.0167 <sup>b</sup> |
| HS diploma or GED                                                                                                                                       | 41,207 (23.7%)                                 | 2,033,010 (38.4%)                        |                     |
| > HS                                                                                                                                                    | 83,011 (47.6%)                                 | 2,546,113 (48.1%)                        |                     |
| Insurance Status                                                                                                                                        |                                                |                                          |                     |
| Uninsured                                                                                                                                               | 27,781 (10.8%)                                 | 311,309 (3.6%)                           | 0.0135 <sup>b</sup> |
| Insured                                                                                                                                                 | 229,273 (89.2%)                                | 8,320,262 (96.4%)                        |                     |
| Region                                                                                                                                                  |                                                |                                          |                     |
| Northeast                                                                                                                                               | 31,446 (11.8%)                                 | 1,430,039 (16.6%)                        | 0.550               |
| Midwest                                                                                                                                                 | 57,106 (21.4%)                                 | 2,097,561 (24.3%)                        |                     |
| South                                                                                                                                                   | 123,289 (46.2%)                                | 3,113,699 (36.0%)                        |                     |
| West                                                                                                                                                    | 54,800 (20.6%)                                 | 1,996,858 (23.1%)                        |                     |
| Reasons for Receiving Delayed Medical Care                                                                                                              | Skin of Color Melanoma Patients<br>(n=266,641) | White Melanoma Patients<br>(n=8,638,157) | P-Value             |
| Unable to get an appointment soon, n (%)                                                                                                                | 49,721 (18.9%)                                 | 711,266 (8.3%)                           | 0.0048 <sup>b</sup> |
| Office/clinic not open, n (%)                                                                                                                           | 14,843 (5.6%)                                  | 259,982 (3.1%)                           | 0.3343 <sup>b</sup> |
| Unable to reach physician/clinic by telephone, n (%)                                                                                                    | 236,957 (12.4%)                                | 32,703 (2.7%)                            | 0.0001 <sup>b</sup> |
| Lacked transportation, n (%)                                                                                                                            | 25,366 (9.6%)                                  | 134,324 (1.6%)                           | 0.0001 <sup>b</sup> |
| Wait too long to see physician, n (%)                                                                                                                   | 27,122 (10.3%)                                 | 331,773 (3.9%)                           | 0.0341 <sup>b</sup> |

Skin of color includes Black, American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, or multiple races

<sup>a</sup>Two-tailed t-test

<sup>b</sup>χ<sup>2</sup> test

are more likely to be Medicaid-insured or be uninsured,<sup>4</sup> it is possible that many may seek care at outpatient dermatology clinics at safety net hospitals.<sup>7</sup> Many of these clinics have long wait times for appointment availability and are understaffed,<sup>7</sup> which may contribute to delays in obtaining care. Furthermore, SOC patients may have difficulty taking leave from work during clinic hours, which may contribute to challenges in acquiring

an appointment.<sup>7</sup> Limitations of this survey-based study include non-response bias and self-reported diagnosis of melanoma. Future research directions may focus on the impact of delayed access to healthcare services on disease burden. As the demographics of the US shift towards a non-white majority,<sup>1</sup> it is crucial for dermatologists to acknowledge obstacles in obtaining timely medical care in SOC individuals.

TABLE 2.

| Multivariable Logistic Regression Analysis of Delays in Access to Medical Care* |                                                      |         |
|---------------------------------------------------------------------------------|------------------------------------------------------|---------|
| Independent Variables                                                           | Dependent Variable:<br>Received Delayed Medical Care |         |
|                                                                                 | aOR (95% CI)                                         | P-Value |
| Race/Ethnicity                                                                  |                                                      |         |
| White                                                                           | 1 [Reference]                                        | --      |
| Skin of Color                                                                   | 2.27 (1.01-5.102)                                    | 0.048   |
| Age                                                                             | 0.98 (0.97-1.00)                                     | 0.021   |
| Insurance Status                                                                |                                                      |         |
| Uninsured                                                                       | 1 [Reference]                                        | --      |
| Insured                                                                         | 0.38 (0.06-2.20)                                     | 0.277   |
| Sex                                                                             |                                                      |         |
| Male                                                                            | 1 [Reference]                                        | --      |
| Annual Household Income                                                         |                                                      |         |
| \$0-\$49,999                                                                    | 1 [Reference]                                        | --      |
| \$50,000-\$99,999                                                               | 1.18 (0.71-1.96)                                     | 0.512   |
| >\$100,000                                                                      | 0.80 (0.41-1.54)                                     | 0.501   |
| Education                                                                       |                                                      |         |
| <HS graduate                                                                    | 1 [Reference]                                        | --      |
| HS diploma or GED                                                               | 0.47 (0.22-0.99)                                     | 0.046   |
| > HS                                                                            | 0.41 (0.18-0.92)                                     | 0.031   |
| Region                                                                          |                                                      |         |
| Northeast                                                                       | 1 [Reference]                                        | --      |
| Midwest                                                                         | 1.20 (0.39-3.67)                                     | 0.746   |
| South                                                                           | 1.42 (0.52-3.86)                                     | 0.495   |
| West                                                                            | 1.40 (0.46-4.25)                                     | 0.552   |

\*Includes those who delayed medical care due to 1) inability to obtain appointment, 2) clinic not open, 3) unable to reach physician/clinic by telephone, 4) lacked transportation, 5) wait was too long to see physician

DISCLOSURES

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AUTHOR CORRESPONDENCE

**April W. Armstrong MD MPH**  
E-mail:..... armstrongpublication@gmail.com

# The Safety of GLP1 Receptor Agonist Usage in Mohs Micrographic Surgery Patients

Margo Schoenberg BS, Ramsay Hafer BS, Vaibhav Garg MD, Stephanie R. Jackson Cullison MD PhD

Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA

To the Editor,

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are widely prescribed for type 2 diabetes and, more recently, for obesity management.<sup>2</sup> With their expanding use, questions have emerged regarding perioperative safety. Delayed wound healing, fat necrosis, and tissue fragility have been described in breast reconstruction, and nausea and vomiting are well-documented perioperative effects.<sup>1,2</sup> To our knowledge, no large-scale study has evaluated postoperative outcomes in dermatologic surgery among patients using GLP1-RAs.

We conducted a retrospective cohort study using TriNetX, a federated health record network including over 130 million patients from more than 70 U.S. healthcare organizations.

Adult patients undergoing Mohs micrographic surgery (MMS) between 2015 and 2025 were identified using CPT codes. Two cohorts were generated: patients with ≥6 months of continuous GLP1-RA use prior to surgery, and patients with no history of GLP1-RA prescriptions. Six months of exposure was chosen based on existing literature suggesting that this threshold reflects peak GLP1-RA effects.<sup>3</sup>

One-to-one propensity score matching was used to balance cohorts by age, sex, race, BMI, diabetes status, cardiovascular risk factors, and immunosuppressive medication use. After matching, each cohort included 4,912 patients. Postoperative outcomes were identified within 60 days of MMS using ICD-

TABLE 1.  
Outcomes Within 60 Days of Mohs Micrographic Surgery in Patients With and Without GLP1-RA Use

| Outcome                         | GLP<br>n (%)      | Controls<br>n(%)  | Odds Ratio<br>(95% CI) | P-value |
|---------------------------------|-------------------|-------------------|------------------------|---------|
| Cellulitis                      | 78<br>(1.59%)     | 71<br>(1.45%)     | 1.100<br>(0.796–1.521) | 0.563   |
| Infections of skin/SQ tissue    | 161 (3.28%)       | 141<br>(2.87%)    | 1.147<br>(0.911–1.443) | 0.242   |
| Disruption of wound             | 35<br>(0.71%)     | 38<br>(0.77%)     | 0.920<br>(0.581–1.459) | 0.725   |
| Hemorrhage                      | 16<br>(0.33%)     | 13<br>(0.26%)     | 1.232<br>(0.592–2.563) | 0.577   |
| Muscle weakness                 | 29<br>(0.59%)     | 17<br>(0.35%)     | 1.710<br>(0.938–3.116) | 0.076   |
| Disturbances of skin sensation* | 80<br>(1.63%)     | 48<br>(0.98%)     | 1.678<br>(1.170–2.405) | 0.004   |
| Rash                            | 36<br>(0.73%)     | 40<br>(0.81%)     | 0.899<br>(0.572–1.413) | 0.645   |
| Swelling/mass/lump              | 38<br>(0.77%)     | 40<br>(0.81%)     | 0.950<br>(0.608–1.483) | 0.820   |
| Hypertrophic scar               | 21<br>(0.43%)     | 24<br>(0.49%)     | 0.874<br>(0.486–1.573) | 0.654   |
| Procedure-related infection     | 37<br>(0.75%)     | 31<br>(0.63%)     | 1.195<br>(0.740–1.929) | 0.465   |
| Mohs additional stage           | 2,109<br>(42.93%) | 2,169<br>(44.15%) | 0.952<br>(0.879–1.031) | 0.222   |
| Nausea/vomiting*                | 117<br>(2.38%)    | 75<br>(1.53%)     | 1.574<br>(1.174–2.109) | 0.002   |

Statistical significance is designated as *P* < .05; all statistically significant values are designated with \*. CI, confidence interval; GLP1-RA, glucagon-like peptide-1 receptor agonist; Intraop, intraoperative; No., number; SQ, subcutaneous.

10 codes for clinical complications and CPT codes consistent with prior administrative data studies.<sup>4</sup> Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using TriNetX analytics.

The matched cohorts were similar across key clinical and demographic variables. The mean age was 68.5 years ( $\pm 9.2$ ) in the GLP1-RA group and 68.6 years ( $\pm 9.6$ ) in the control group. The majority were male (61.4% vs 62.5%) and White (94.9% vs 96.0%). Rates of obesity were also similar between groups, with 66.2% of GLP1-RA users and 65.9% of controls having BMI  $>30$ . Diabetes mellitus was present in 87.6% of GLP1-RA users and 87.5% of controls. Other comorbidities such as nicotine dependence (12.7% vs 12.2%), hypothyroidism (23.6% vs 23.7%), and use of anticoagulants (53.0% vs 53.3%) or immunosuppressive medications were well matched, with all standardized differences  $<0.05$ .

Within 60 days of Mohs micrographic surgery, GLP1-RA users were more likely than controls to experience disturbances of skin sensation (1.63% vs 0.98%; OR 1.68, 95%CI 1.17–2.41;  $P=.004$ ). Postoperative nausea and vomiting, a known adverse effect of GLP1-RA therapy, was also more common (2.38% vs 1.53%; OR 1.57; 95% CI 1.17–2.11;  $P=.002$ ). No significant differences were observed for cellulitis, infections of skin and subcutaneous tissue, wound disruption, hemorrhage, rash, swelling, hypertrophic scar formation, or the need for additional stages or blocks during MMS (all  $P>0.05$ ). Rare complications including pigmentary changes, gangrene, skin graft complications, intraoperative or postoperative hemorrhage, hematoma, and seroma each occurred in  $\leq 0.4\%$  of patients and did not differ significantly between groups. Rates of intralesional injection and procedure-related infection were also comparable.

The observed increase in postoperative sensory disturbance may indicate subtle perioperative effects of GLP1-RAs, though the clinical significance remains unclear. GLP1-RAs have been reported to influence peripheral nerve signaling in other contexts, such as diabetic neuropathy, through combined metabolic and anti-inflammatory mechanisms.<sup>5</sup> Whether these effects underlie the sensory findings after dermatologic surgery is unknown and warrants further study. The increased incidence of nausea and vomiting, a well-recognized effect of GLP1-RA therapy, provides internal validity and supports the accuracy of outcome detection. These findings support the continued use of GLP1-RAs in dermatologic surgery, while highlighting the need for further studies exploring formulation-specific risks, perioperative symptom management, and potential sensory effects.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

**Data Availability Statement:** Data is available through the online dataset: <https://live.trinetx.com/>

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## AUTHOR CORRESPONDENCE

### Stephanie Jackson MD

E-mail:..... stephanie.jackson@jefferson.edu

# Topical Vehicle Design: Educational Intervention Addresses Gap in Dermatology Resident Training

Nikkia Zarabian BS, Mina Farah BA, Kaylee Fisher BA, Savanna I. Vidal BS, Nikita Menta BA, Yagiz Matthew Akiska BSE, Adam Friedman MD FAAD

Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC

## INTRODUCTION

Over-the-counter (OTC) products are often used as first-line or adjunctive treatments for many dermatologic conditions.<sup>1,2</sup> Topical formulations consist of one or more active ingredients combined with a vehicle, which influences stability, ability to permeate the skin barrier, and optical and physical properties of the product.<sup>3</sup> Topical vehicles (TVs), including ointments, creams, gels, and foams, differ in their pharmacological properties and consequently influence tolerability, patient adherence, and overall treatment success.<sup>3-5</sup> Thus, it is crucial that clinicians, especially dermatologists, are adequately trained on TV formulations. This study sought to quantify TV training in dermatology residency and to evaluate the impact of a targeted educational intervention on residents' overall knowledge and their confidence in recommending and discussing TV formulations and OTC products.

## MATERIALS AND METHODS

An IRB-approved, anonymous survey (IRB#NCR256476) was distributed to dermatology residents from three training programs in Washington, DC, who attended the inaugural "Lab-to-Label: Science and Clinical Application in Sunscreen and Cosmeceutical Vehicles" conference. The educational intervention included didactic lectures, multidisciplinary

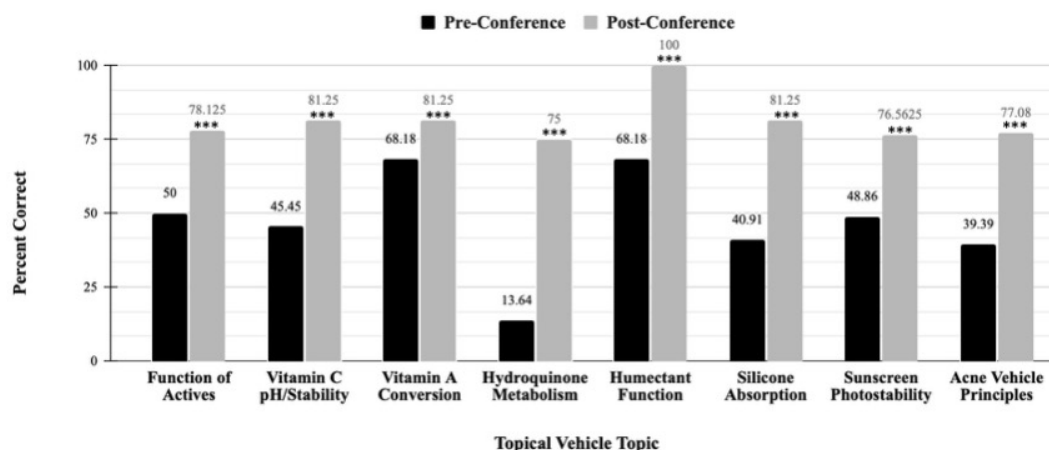
panel discussions, and hands-on tactile product evaluation. Conference content addressed skin structure and function, TV chemical science, OTC product categories and ingredients, FDA regulations, formulation considerations for acne and sunscreen therapies, and navigation of skincare trends and the influence of social media on patient education.

Participants completed pre- and post-conference surveys assessing prior exposure to TV education, comfort discussing TV formulations, confidence recommending OTC products based on TV type, and formulation knowledge. Objective questions evaluated resident knowledge of actives, vitamin C, vitamin A derivatives, hydroquinone, humectants, silicones, sunscreen, and acne topicals. Pre- and post-intervention objective knowledge scores were compared using a paired-samples t-test in SPSS version 31 ( $\alpha=.05$ ).

## RESULTS

Of the 22 dermatology residents present, 17 participated in the pre- and post-surveys (77% response rate). Most respondents (81.8%) reported no formal training in cosmetic chemistry or TV formulation. Pre-survey responses indicated that only 13.6% felt "very comfortable" and 31.8% felt "somewhat comfortable"

**FIGURE 1.** Topical vehicle objective knowledge scores pre- and post-conference. \*\*\* $P<.001$  indicates statistically significant difference.



discussing TVs with patients. After the educational intervention, 81% reported feeling “*much more comfortable*” discussing differences between TV formulations. Similarly, confidence in recommending OTC products based on TV formulations also improved markedly. Pre-intervention, 4.6% felt “*very confident*,” and 36.4% felt “*somewhat confident*” recommending OTC products based on TV formulations. Post-conference, 81.3% reported feeling “*much more confident*.” Objective knowledge scores also improved across all categories (Figure 1). A paired-samples t-test demonstrated a statistically significant increase ( $P<.001$ ) in accuracy from pre-survey to post-survey, with the assumption of normality confirmed using a Shapiro-Wilk test ( $P=.155$ ).

## DISCUSSION

Dermatology residents across three different programs exhibited limited formal training in TV formulation science, highlighting the breadth of this knowledge gap. However, they demonstrated rapid and significant improvement in comfort, confidence, and foundational knowledge following a targeted educational intervention. The “Lab-to-Label” conference resulted in the majority of dermatology residents feeling more comfortable discussing TV formulation differences with patients and more confident recommending OTC products based on TV formulation. Consistent improvement across comfort, confidence, and objective knowledge domains suggests a meaningful benefit to incorporating standardized TV education and educational conferences into dermatology training. Future studies should evaluate long-term retention and examine whether comparable educational interventions could also benefit practicing dermatologists. Limitations of this study include its small regional sample size and the reliance on self-reported measures.

## DISCLOSURES

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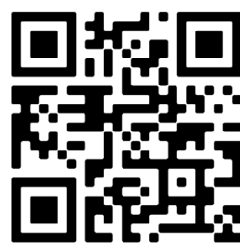
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## AUTHOR CORRESPONDENCE

**Adam Friedman MD FAAD**

E-mail:..... ajfriedman@mfa.gwu.edu

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## NEWS, VIEWS, AND REVIEWS

### The State of Primary Hyperhidrosis: Therapeutic Advancements and National Representation

Nikkia Zarabian BS, Mina Farah BA, Caroline Clark MD, Emily Nadelmann MD FAAD, Adam Friedman MD FAAD

Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC

#### INTRODUCTION

Hyperhidrosis (HH) is defined as excessive sweating beyond the physiologic requirements of thermoregulation.<sup>1</sup> HH is classified as either primary (idiopathic) or secondary to an underlying medical condition or medication.<sup>1</sup> Primary hyperhidrosis (PHH), the most common form of HH, affects nearly 93% of patients with HH and 2.8–4.8% of the U.S. population.<sup>1,2</sup> Although the exact pathophysiology of PHH is unknown, it is proposed to result from overstimulation of cholinergic receptors on eccrine sweat glands concentrated in the axilla, face, palms, and soles, as well as an impaired acetylcholine negative feedback loop.<sup>3</sup> A genetic predisposition has also been suggested, as 30–60% of patients with PHH report a positive family history.<sup>1</sup>

The diagnosis of PHH is primarily clinical and relies on a comprehensive history and physical examination. Diagnostic criteria include excessive sweating for at least six months without apparent cause, and at least two of the following criteria: symmetrical bilateral distribution, occurrence at least once a week, age of onset prior to 25 years, positive family history, disruption of daily activities, and absence of nocturnal sweating.<sup>4</sup> PHH can have a profound psychosocial impact, with nearly 48% of patients reporting a poor or very poor quality of life and higher rates of depression and anxiety compared to the general population.<sup>1</sup> Disease management is also burdensome, with reports of patients spending approximately 15–60 minutes per day managing symptoms.<sup>1</sup>

Further complicating the patient experience, HH has historically been underrecognized and undertreated due to limited awareness among the public and within medical communities, which perpetuates its ongoing stigmatization.<sup>5</sup> Delays in care-seeking are common, with nearly half of patients reporting that they waited 10 years or longer before seeking medical attention.<sup>6</sup> In a study of 511 patients with HH, 36.8% reported a diagnostic delay exceeding ten years.<sup>7</sup> In another study of over 8,000 individuals with HH, only 51% reported discussing their condition with a healthcare practitioner, primarily due to a lack of awareness that HH is a medical condition, followed by unfamiliarity with available treatment options.<sup>2</sup>

Given the significant psychosocial burden and longstanding underrecognition of HH, continued advancement in therapeutic options and increased public and professional awareness are essential for improving disease management and reducing stigma. As such, this paper provides an overview of recent updates to the US Food and Drug Administration (FDA)-approved treatments for

HH and examines the representation of HH across major national dermatology podiums over the past year.

#### Updates in FDA-Approved Treatments for PHH

Management strategies for PHH vary based on disease location and severity and may include topical treatments (antiperspirants and anticholinergics), systemic medications (oral anticholinergics, adrenergic modulators), device-based therapies (iontophoresis, microwave thermolysis), injectable options (botulinum toxin), and surgical interventions (sympathectomy, excision, liposuction/curettage).<sup>1</sup> Over the past decade, the FDA has approved two new topical pharmacologic treatments for PHH, including glycopyrronium tosylate (GT) and sofpironium bromide (SB) topical gel.

In 2018, the FDA approved topical GT for the treatment of primary axillary hyperhidrosis (PAH) in patients aged 9 years and older.<sup>8</sup> GT is administered once daily using a pre-moistened cloth containing 2.4% glycopyrronium (equivalent to 3.75% GT), which competitively blocks muscarinic acetylcholine receptors on sweat glands, thereby reducing sweat production.<sup>1,8</sup> Two phase III randomized, double blind, vehicle-controlled clinical trials, ATMOS-1 (n=344) and ATMOS-2 (n= 353), evaluated the efficacy and safety of 2.4% glycopyrronium applied once daily to both axillae for four weeks.<sup>8</sup> Both trials demonstrated significant reductions in patient-reported severity of axillary sweating, with improvements observed as early as week one.<sup>8</sup> Treatment-emergent adverse events (TEAEs) were reported in 33.9% of GT-treated patients in ATMOS-1 and 44.0% in ATMOS-2. Most TEAEs were mild to moderate and transient, including dry mouth, mydriasis, blurry vision, urinary hesitancy, and application site reaction.<sup>8</sup>

In 2024, the FDA approved SB 15% (12.45% sofpironium) gel, another topical anticholinergic therapy, for PAH in patients aged 9 years and older.<sup>9</sup> SB was developed using a retro-metabolic drug design, allowing rapid inactivation into non-toxic metabolites after exerting a local therapeutic effect. This strategy aimed to increase localized efficacy and reduce adverse effects.<sup>9</sup> Two multicenter, randomized, vehicle-controlled, phase III clinical trials, CARDIGAN-1 (n=350) and CARDIGAN-2 (n=351), evaluated its efficacy and safety in patients with PAH.<sup>9</sup> At day 43, nearly 49% of SB-treated patients in CARDIGAN-1 and 64% of SB-treated patients in CARDIGAN-2 achieved a  $\geq 2$  point reduction in the Hyperhidrosis Disease Severity Measure-Axillary, 7-item scale (HDSM-Ax-7).<sup>9</sup> TEAEs were reported in 35.8% of SB-treated patients in CARDIGAN-1 and 45% in CARDIGAN-2

and included blurred vision, dry mouth, mydriasis, urinary retention, dry eyes, constipation, and local site reaction.<sup>10</sup> Again, the majority of these were mild to moderate and resolved after discontinuation.<sup>9</sup>

Despite promising results demonstrating efficacy in PHH treatment, GT and SB are only approved for PAH. There remains a substantial unmet need for effective treatments of non-axillary sites or severe disease that is not adequately controlled with topical therapy. Additionally, anticholinergic adverse effects may limit tolerability and adherence in some patients.

### National Representation

In addition to therapeutic advancements, continuing medical education of board-certified dermatologists and trainees regarding HH and its management is critical. While national dermatology conferences often provide educational sessions on inflammatory skin diseases, skin cancer, and aesthetic procedures, HH remains underrepresented. A review of agendas from 10 of the largest U.S. dermatology conferences over the past year demonstrated that only three included dedicated HH sessions (Table 1). Among the three meetings, each offered only a single session, despite the total number of sessions ranging from approximately 90 to over 300 sessions.

HH has a prevalence comparable to that of psoriasis (~3%), a condition consistently represented at national meetings.<sup>11</sup> The relative paucity of HH-focused programming underscores the need for increased representation of HH and highlights an underutilized opportunity for clinicians to gain valuable educational exposure.<sup>11</sup> Given the expanding therapeutic landscape for PHH, including two FDA approvals within the past decade, limited podium representation at national dermatology meetings may reflect the historical underrecognition of HH.<sup>5</sup> With growing evidence affirming HH as a highly prevalent and burdensome disease state, greater inclusion of HH at national meetings is warranted to ensure clinicians remain informed to better validate the patient experience.

**Table 1.** Representation of hyperhidrosis at major US dermatology conferences within the past year (February 2025 – February 2026).

| Meeting                                                 | Inclusion of Hyperhidrosis in Agenda | Number of Sessions on Hyperhidrosis |
|---------------------------------------------------------|--------------------------------------|-------------------------------------|
| Dermsquared 2025 Winter Clinical Dermatology Conference | No                                   | N/A                                 |
| American Academy of Dermatology 2025 Annual Meeting     | Yes                                  | 1                                   |
| Music City SCALE 2025                                   | Yes                                  | 1                                   |
| Las Vegas Dermatology Seminar 2025                      | No                                   | N/A                                 |
| Dermsquared 2025 Fall Clinical Dermatology Conference   | No                                   | N/A                                 |
| Mount Sinai 2025 Winter Symposium                       | No                                   | N/A                                 |
| Maui Derm Hawaii 2026                                   | No                                   | N/A                                 |
| ODAC Dermatology Conference 2026                        | No                                   | N/A                                 |
| 2026 South Beach Symposium                              | Yes                                  | 1                                   |
| Masterclasses in Dermatology 2026 Annual Meeting        | No                                   | N/A                                 |

In efforts to increase knowledge within the medical community, the International Hyperhidrosis Society (IHHS) has expanded its educational and outreach initiatives to provide comprehensive information and resources from leading experts in the field.<sup>5</sup> The IHHS provides detailed overviews of treatment options that may be easily referenced by patients and providers to ultimately help address persistent gaps in care.<sup>5</sup>

### CONCLUSION

Despite its prevalence and substantial psychosocial impact, HH remains historically underrecognized, undertreated, and stigmatized. Over the past decade, two new FDA-approved topical anticholinergic therapies have emerged for PHH. However, both are limited to approval for axillary disease, highlighting a significant unmet need for patients with multifocal involvement, non-axillary disease, or inadequate response to topical therapies. Additionally, limited focus on HH and its management in the agendas of major U.S. dermatology conferences underscores an important opportunity to enhance clinician education, increase awareness, and expand visibility of HH in academic and professional forums.

### DISCLOSURES

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### AUTHOR CORRESPONDENCE

**Adam Friedman MD FAAD**

E-mail:..... ajfriedman@mfa.gwu.edu

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