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JOURNAL OF DRUGS IN DERMATOLOGY

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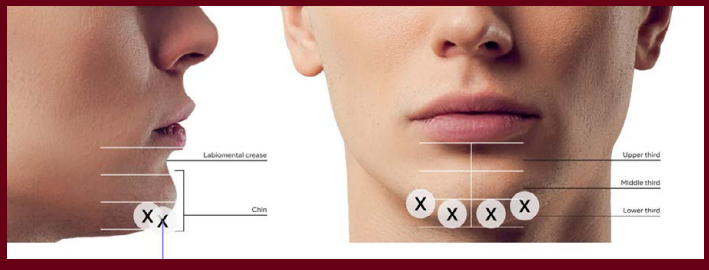

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Management and Prevention of Neuromodulator Complications

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ABSTRACT

The use of neuromodulators for cosmetic purposes has a remarkable safety record; nevertheless, unwanted effects can and do sometimes occur when neurotoxins are used for facial rejuvenation, such as neutralizing antibodies and eyelid ptosis. The primary objective of the following roundtable discussion was to review the most commonly reported complications from neurotoxins and summarize considerations for reducing the risk of complications. A roundtable discussion was held by 5 notable experts in their field during a special addition of the *Thriving in Diversity* webinar series on Thursday, February 15, 2024. Three presenters were provided with an opportunity to share their knowledge. Common complications associated with the use of neuromodulators include lack of response due to neutralizing antibody formation and eyelid ptosis. Common complications, such as neutralizing antibodies, can often be prevented by avoiding known risk factors. The use of topical alpha adrenergic agonists can often improve the appearance of eyelid ptosis. The cosmetic use of neuromodulators remains extremely safe, and serious adverse events rarely occur.

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INTRODUCTION

The demand for cosmetic surgical procedures has continued to increase in recent years. Compared with pre-pandemic statistics, the overall number of procedures increased by 19% from 2019 to 2022.[1] Among minimally invasive procedures, the injection of neuromodulators has been by far the most prevalent and shown the greatest change, increasing from 5,043,057 procedures in 2018 to 8,736,591 in 2022, a 73% increase.[1] The use of neuromodulators for cosmetic purposes has a remarkable safety record. Serious adverse events from approved products, such as suspected toxin-related anaphylaxis are extremely rare,[2] and reports of toxin spread,[3] or iatrogenic botulism, have only been associated with medical uses, such as cervical dystonia.[4,5] Nevertheless, unwanted effects can and do sometimes occur when neurotoxins are used for facial rejuvenation, such as neutralizing antibodies,[6] facial flaccidity,[7] and eyelid ptosis.[8]

Objectives

The objectives of the roundtable discussion were to describe the most commonly reported complications from neurotoxins; consider manufacturing and product differences of the most popular neurotoxins and how this may influence the safe use for aesthetic treatments; discuss effective communication channels, styles, and listening skills for patients experiencing complications; and summarize considerations for reducing the risk of complications.

MATERIALS AND METHODS

A roundtable discussion was held by this manuscript's authors, 5 notable experts in their field during a special addition of the Thriving in Diversity webinar series on Thursday, February 15, 2024.[9] Three presenters were provided an opportunity to share their knowledge while they and other experts responded to audience questions. This activity was planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of FabDay LLC and Advancing Knowledge in Healthcare (AKH, Inc.), which provided activity accreditation.

DISCUSSION

Neutralizing Antibodies

The injection of neuromodulators is by far the most prevalent among minimally invasive procedures[1] and, while it has an undisputed safety record, treatment failures occasionally occur. The successful use of aesthetic botulinum toxin injections is occasionally hindered by immunogenic and non-immunogenic causes. Reasons for non-immunogenic treatment failure include underdosing, poor injection technique, and over-aggressive product reconstitution;[10,11] while immunogenic treatment failure is caused by neutralizing antibodies that have formed against the active toxin or associated complexing proteins.[12] The roundtable discussion began with a presentation by one

of the speakers (JC) of a case of secondary clinical resistance to three Health Canada-approved types of botulinum toxin A (BoNT-A), namely onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA.

This was a 40-year-old white female with 4 prior neuromodulator treatment sessions of the glabella complex consisting of onabotulinumtoxinA (n=2), abobotulinumtoxinA (n=1), and incobotulinumtoxinA (n=1). She initially achieved a good treatment response but developed a diminished response with subsequent treatments. Following her last injection of the glabella (30 U) and horizontal forehead lines (10 U), she developed urticarial wheals at the injection sites with no clinical response after 3 weeks. She underwent testing for suspected secondary nonresponsiveness and failed the Borodic Frontalis Test.[13] The subject in this case was subsequently treated by one of the other roundtable presenters (SF) with botulinum toxin B (rimabotulinumtoxinB) on the glabella (3000 U), lateral canthal lines (375 U), and frontalis (1125 U), with excellent results. Taken together, it was concluded the patient described in the above case report was a secondary non-responder. She achieved a good response with BoNT-B as onabototulinumtoxinA and rimabotulinumtoxinB only share 30% heavy chain homology in their molecular structure.

An alternative to the Borodic Frontalis Test is the Extensor Digitorum Brevis (EBD) test with an electromyogram.[14] The EDB test is a simple quantitative method of detecting resistance to botulinum toxin-A and was used in the patient described above. In this test, 20 units of BoNT-A were injected into the extensor digitorum brevis muscle on the dorsal side of the foot. Using electromyography, her mean baseline compound muscle action potential (CMAP) following peroneal nerve stimulation was 8.2 mV (normal ≥2 mV). After 30 days, the CMAP was essentially unchanged (7.9 mV). As the expected decrease in CMAP of a responsive individual would be at least a 50% reduction, the <20% reduction suggests blockade by neutralizing antibodies. Additional immunologic testing includes direct measurement of neutralizing antibodies;[15] however, the mouse bioassay[12] and immunoprecipitation assay[16] are primarily research tools that are relatively unavailable to most clinicians, expensive, and have limited sensitivity.

Primary nonresponsiveness can also be a cause of neuromodulator treatment failure. Reasons for this include neuromuscular disorders, such as myasthenia gravis, poor injection technique, or reduced BoNT-A potency due to inadequate storage and improper reconstitution.[10,11,17] Genetic variability is another possibility. During a discussion of nonresponsive patients encountered by the roundtable participants, it was observed that these patients were primarily of Middle Eastern (n=3) and Mediterranean (n=1) origin, suggesting a possible genetic association.

Secondary nonresponsiveness is characterized by intentional immunization,[18] or treatment failure following initial successes with antibody formation against the 150 kD neuromodulator core protein, the binding domain, or the accessory proteins.[15] A large meta-analysis in 2010 showed only 11 of 2,240 subjects (0.5%) treated with onabotulinumtoxinA for 5 different indications developed neutralizing antibodies against BoNT-A.[15] When subjects only treated on the glabella were assessed, only 2 of 718 subjects (0.3%) developed neutralizing antibodies.

A more recent meta-analysis of neutralizing antibody formation against onabotulinumtoxinA was performed across multiple indications including cervical dystonia, post-stroke spasticity, axillary hyperhidrosis, neurogenic overactive bladder, and glabellar lines.[19] The study found that among evaluable subjects, 27 of 5,876 (0.5%) developed neutralizing antibodies after onabotulinumtoxinA treatment. Due to their low incidence, no evidence of a relationship was apparent between the presence of neutralizing antibodies and gender, treatment indication, dose, dosing interval, treatment cycle, or the injection site. Subjects who developed neutralizing antibodies had no immunological disorders.

One participant (MK) encountered a patient from an unrelated practice who became nonresponsive after receiving small doses of BoNT-A approximately every 2 weeks for 2 years, which were deemed to be essentially vaccinating doses. It was suggested that patients should be discouraged from returning to the clinic too soon after treatment unless there is a significant cosmetic reason, such as an asymmetric brow.

Risk factors for developing neutralizing antibodies include high doses of neuromodulator per treatment (eg, 400 to 500 U for cervical dystonia), booster injections 2 weeks after primary treatment which is analogous to immunization, and the use of products with containing accessory proteins (eg, onabotulinumtoxinA, abobotulinumtoxinA, nivoboltulinumtoxinA) vs those containing the core 150 kD molecule (eg, daxibotulinumtoxinA, incobotulinumtoxinA).[20,21]

Patients who are nonresponsive to BoNT-A may respond to a type-B toxin. Among 36 patients with cervical dystonia and a secondary non-response to type-A toxin, 13 (36%) had an acceptable clinical response to rimabotulinumtoxinB and were able to continue therapy. Among 20 patients with spasticity who were nonresponsive to type-A, 7 responded to rimabotulinumtoxinB.[22] For subjects becoming nonresponsive, response may return after waiting 30 months (personal communication Dr J Jankovic).

Treating Ptosis Following BoNT-A Injection

Blepharoptosis is the name of the condition that occurs when a misplaced BoNT-A injection causes the upper eyelid to droop.

TABLE 1.

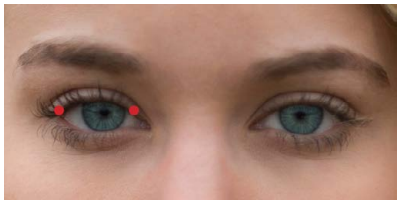
Ophthalmic Drops for Treating Ptosis	
Aproclonidine 0.5%	Iopidine®, Alcon Laboratories, Inc., Fort Worth, TX
Oxymetazoline 0.025%	Visine® LR, J & J Healthcare Products Inc., New Brunswick, NJ
Naphazoline 0.03%	Clear Eyes®, Prestige Consumer Healthcare Inc., Lynchburg, VA
Naphazoline 0.025%/ Pheniramine 0.3%	Naphcon-A®, Alcon Laboratories, Inc., Fort Worth, TX

For some patients, this may represent a significant cosmetic deficit. The simplest means to provide some correction is to stimulate Müller's muscle. This is a sympathetically innervated smooth muscle that originates from the under surface of the levator aponeurosis at the level of the Whitnall ligament and inserts into the superior border of the tarsus. It contributes ~2 mm of eyelid elevation.

Stimulating Müller's muscle can be done with one of several available topical alpha adrenergic agonists (Table 1). Apraclonidine 0.5% is a prescription eyedrop indicated to control or prevent post-surgical elevations in intraocular pressure that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy.[23] It is effective but not recommended for treating Müller's muscle unless intraocular pressure can be monitored. Several other eyedrops are available over-the-counter, such as oxymetazoline and naphazoline, with and without an antihistamine. As they do not provide long-lasting relief, patients should choose when they wish to use them.

Another means for treating ptosis is to inject BoNT-A into the orbicularis oculi (Figure 1). This is a circular muscle consisting of the preseptal, pretarsal, and orbital orbicularis. Contraction of this muscle is responsible for gentle and forced closure of the eyelid, and this is the only muscle capable of doing so. Inject the far medial and far lateral pretarsal orbicularis oculi with one-half or one-third unit of BoNT-A. Anecdotally, this presenter (MK) is aware of others who also inject the orbital orbicularis at the 12-o'clock position but has never encountered the need to do so because of the horizontal orientation of muscle fibers in that area.

FIGURE 1. A means for treating ptosis is to inject BoNT-A into the far medial and far lateral pretarsal orbicularis oculi with one-half or one-third unit of BoNT-A. Injections should be made 1 mm to 2 mm above the lid margin.



It was agreed in general that using lower volumes/higher concentration of BoNT-A lessened the likelihood of unwanted ptosis; however, one participant (MK) uses relatively dilute solution (100 U/4 mL) but uses a greater number of precise injection points to control the desired effect.

Audience Questions and Answers

Toxin Spread Causing Harm

A question was put to the roundtable regarding their experience with toxin spread. Distant spread has never been observed by the roundtable participants; however, everyone recalled the "BoNT-A disaster" that occurred in 2004 involving the use of improperly diluted raw animal research botulinum toxin in milligram vials (not mouse unit vials).[24] Several individuals were hospitalized requiring ventilatory support. Purchasing neuromodulators from unapproved sources is not recommended.

Current Medical Conditions

Participants agreed that they definitely will not inject patients with myasthenia gravis or Lambert Eaton myasthenic syndrome.[25] Toxin injections during pregnancy are probably not worrisome,[26] but cosmetic injections are not necessary to perform. Also acknowledged is that many treated women may not be aware they are pregnant. Similarly, treating patients who are lactating is probably okay, but one participant recommends that their patients "pump and dump" their breastmilk for 24 hours as a precaution. Intravenous aminoglycosides are not concerning as that scenario is unlikely to occur in the clinic. One participant encountered a patient currently undergoing treatment with a new immunotherapy for cancer. That patient did not receive BoNT-A based on hypothetical concerns for a potential interaction with her cancer treatment.

Is Supplemental Zinc Recommended?

This question was in reference to past suggestions that zinc supplementation can increase the degree and duration of BoNT-A preparations used for cosmetic purposes;[27] however, the current evidence for this is not compelling[28] and zinc supplementation is not recommended.

Bone Loss from Masseter Injections

Targeted atrophy of the masseter is a popular procedure among diverse populations and especially patients of East Asian descent.[29] Is bone loss a concern? It was speculated that it might be expected to occur due to reduced bite force, but it has not been observed.[30] It was looked for in a phase 2 masseter study with dental exams and CT scans.[31]

CONCLUSION

The cosmetic use of neuromodulators is extremely safe in educated hands and serious adverse events are rare. Uncommon complications such as neutralizing antibody formation can often be prevented by avoiding known risk factors, such as reinjecting

a short time after the initial treatment. The use of topical alpha adrenergic agonists can often improve the appearance of transient eyelid ptosis.

DISCLOSURES

Steven H. Dayan MD is a consultant to Allergan Aesthetics, Galderma, Merz Aesthetics®, Evolus, Inc., and Endo Pharmaceuticals; is on the speaker's bureau for Allergan Aesthetics, Galderma, and Merz Aesthetics®, Chroma, and Endo Pharmaceuticals; and has received grants and research support from Allergan Aesthetics, Galderma, Merz Aesthetics®, Teoxane, Endo Pharmaceuticals, and Croma Pharma®; and a stockholder in Revance Therapeutics.

Sabrina Fabi MD has received consulting fees from AbbVie, Inc., Galderma, Merz Aesthetics®, Revance Therapeutics, Inc., Endo Pharmaceuticals, Croma Pharma®, L'Oreal Groupe, Ortho Dermatologics, and RoC® Skincare; is on the speaker's bureau for AbbVie, Inc., Galderma, and Merz Aesthetics®, and has received grants or research support from AbbVie, Inc., Galderma, Merz Aesthetics®, Symatese Aesthetics, Endo Pharmaceuticals, Croma Pharma®, Teoxane, and Raziel Therapeutics; and is a stockholder in Allergan Aesthetics, and Revance Therapeutics.
Nowell Solish MD has been a researcher for Galderma, Mera Pharmaceuticals, Inc., AbbVie, Medytix, Revance Aesthetics; and has been a speaker for Galderma, Mera Pharmaceuticals, Inc., AbbVie, Medytix, and Revance Aesthetics.

Jean Carruthers MD has served as a consultant and researcher for Akorn Pharmaceuticals, Alastin Skincare, Appell, Allergan Aesthetics (an AbbVie Corporation), Avari Medical, Bonti, Inc. (now with Allergan/AbbVie), Del Nova, Evolus, Inc., Fount Bio, Inc. (stock options), InMode, InverseGenomic Ltd, Jeune Inc, Merz Aesthetics®, QuantifiCare, Revance Aesthetics, Object Pharma, Inc., and SoftWave Tissue Regeneration Technologies; and served as author and editor for Elsevier; author for *Up to Date:* Neuromodulators and Fillers; assistant editor for *Dermatologic Surgery*; and reviewer for *The Aesthetic Surgery Journal*, *Ophthalmic Plastic and Reconstructive Surgery*, and *Plastic and Reconstructive Surgery.*

Michael Kane MD has served on the advisory board for Allergan Aesthetics, Neothetics, Kythera, Merz Aesthetics®, Revance Aesthetics, Stiefel Laboratories Inc., Galderma; been a consultant for Allergan Aesthetics, Endo Pharmaceuticals, Inc., Evolus, Inc., Ipsen, TauTona/Aline (noe Allergan Aesthetics), L'Oreal Groupe, Alphaeon Corporation, Musculoskeletal Transplant Foundation (now MTF Biologics), Premier Pharma, Valeant Pharmaceuticals, Hancock Jaffe Laboratories, Neothetics, Beiersdorf, Kythera, Teoxane, Merz Aesthetics®, Canfield Scientific, Inc., Shire (now Takeda Pharmaceutical Company), Revance Aesthetics, and Galderma; is the founder of HLA Technolgies (equity); has received honoraria from Galderma and Allergan Aesthetics; has served as an investigator for Coapt, Musculoskeletal Transplant Foundation (now MTF Biologics), Symic Bio Inc., Neothetics, Kythera, Teoxane, Merz Aesthetics, Revance Aesthetics, Galderma; is an investor in White Five Partners; was a speaker for Merz Aesthetics®, Revance Aesthetics, Galderma, Allergan Aesthetics; and has received stock options from Alphaeon (now Aeon Biopharma, Inc.) and Revance Aesthetics.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Exosomes in Cosmetic Dermatology: A Review of Benefits and Challenges

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ABSTRACT

Background: Exosomes are small extracellular vesicles (30-150 nm in size) that play a critical role in cellular communication, transporting proteins, lipids, and nucleic acids between cells. This literature review focuses on evaluating the potential benefits and limitations of exosomes in enhancing skin health and aesthetics through indications such as skin rejuvenation, hair restoration, and pigmentation disorders.

Methods: A thorough literature search was conducted on PubMed using specific MeSH, including "exosomes," "aesthetics," "cosmetic dermatology," "skin rejuvenation," "hair growth," and "wrinkle reduction." The search was limited to free-access studies published in various countries within the last ten years (2014-2024). As a result, a total of 56 relevant references were identified and reviewed to support the discussion.

Results: There are currently no US Food and Drug Administration (FDA) approved exosomes. This review highlights exosomes' potential in skin rejuvenation through extracellular matrix production and matrix metalloproteinases (MMP) inhibition, as well as in hair restoration by stimulating follicle cell activity and modulating inflammation. Despite these benefits, challenges remain, including inconsistent isolation methods, source variability, and the need for clinical trials to confirm long-term safety and efficacy. The regulatory landscape is evolving, and further research is essential to meet standards before exosomes can be broadly adopted in cosmetic dermatology.

Conclusion: While exosomes hold significant potential for non-invasive cosmetic dermatology, there are challenges that need to be addressed, including the standardization of exosome isolation and characterization, the establishment of safety profiles, and the conduct of extensive clinical trials.

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INTRODUCTION

Exosomes, a specific subtype of extracellular vesicles (EVs) ranging from 30 to 150 nanometers, have emerged as powerful tools in intercellular communication, transporting proteins, lipids, and nucleic acids between cells.[1] Their potential applications in the field of aesthetics and cosmetic dermatology have garnered significant attention due to their ability to influence a variety of cellular processes, including skin rejuvenation and hair restoration. These nanoscale vesicles, formed within the endosomal system of cells, play a critical role in paracrine signaling by effectively delivering bioactive molecules to target cells and modulating their function. Exosomes are naturally produced by a wide variety of cell types, each contributing unique bioactive molecules to these vesicles. Their sources include platelets, mesenchymal stem cells (MSCs), immune cells, epithelial cells, and even plant cells, termed plant-derived extracellular nanoparticles (PDENs), each of which imparts distinct properties to the exosomes.[2–5] Recent research has highlighted the utility of exosomes, especially as a cell-free alternative to traditional regenerative therapies. This has led to a surge in studies exploring their efficacy in clinical and preclinical settings, particularly in plastic and reconstructive surgery, wound healing, and skin care.[6,7] Despite the growing interest and promising early results, the use of exosomes remains under stringent regulatory scrutiny. In the US, for instance, the FDA has not yet approved any exosome-based products for clinical use, largely due to concerns about their safety, purity, and batch-to-batch consistency.[8] Similarly, in Europe, strict regulations limit the use of human-derived exosomes, pushing researchers to explore plant-

based exosomes as an alternative.[9] This literature review aims to provide a comprehensive overview of the current state of research on the application of exosomes in cosmetic dermatological procedures. It will critically analyze existing studies to elucidate the potential benefits and limitations of exosome-based therapies, particularly in skin rejuvenation and hair restoration. Given the nascent stage of exosome research, mapping the literature on this topic is crucial to establishing future guidelines.

MATERIALS AND METHODS

A thorough search was conducted on PubMed using keywords MeSH such as "exosomes," "aesthetics," "cosmetic dermatology," "skin rejuvenation," "hair growth," and "wrinkle reduction." Only free-access studies published within the last ten years (2014-2024) around the globe were included. A total of 221 studies were initially identified. After removing duplicates and screening titles and abstracts, 104 studies were selected for full-text review. Upon detailed examination of the full manuscripts, 20 studies were excluded due to lack of relevance to cosmetic dermatology, with some studies being more focused on general dermatology topics, as well as methodological flaws or insufficient data. Ultimately, 56 studies were deemed relevant and were included in the review to support the arguments made.

Exosomes in Regenerative Medicine

Exosomes are pivotal in facilitating intercellular communication, which is crucial for regenerative processes. These EVs deliver a diverse array of biomolecules, including proteins, RNAs, and lipids, which influence the behavior of recipient cells.[2,10–15] For example, exosomal miRNAs have been shown to modulate gene expression in target cells, thereby promoting tissue repair and regeneration.[16] Furthermore, exosomes derived from mesenchymal stem cells (MSCs), sourced from adipose tissue, bone marrow, umbilical cord, or placenta, exhibit significant immunomodulatory effects.[17] They can alter immune responses by interacting with immune cells, potentially reducing inflammation and facilitating an environment conducive to tissue repair.[17,18] Preclinical studies have demonstrated that MSC-derived exosomes can suppress pro-inflammatory cytokines and enhance the regenerative process, particularly in wound healing and in managing inflammatory diseases. Additionally, exosomes encourage cell proliferation and differentiation, a key aspect of regenerative medicine.[19] They carry growth factors and signal molecules that trigger these processes in recipient cells. They can be found in a wide array of both biological and non-biological sources, each offering unique applications in medical science.[20] MSCs are particularly noted for their regenerative capabilities, extensively utilized in tissue repair and immune modulation. Other stem cell sources, such as induced pluripotent stem cells (iPSCs), produce exosomes that hold promise in tissue regeneration and neuroregenerative therapies, circumventing the ethical issues associated with embryonic stem cells.[21] Immune cell-derived exosomes, such as those from dendritic cells, are pivotal in cancer immunotherapy, capable of carrying tumor antigens to elicit immune responses. Conversely, cancer cell-derived exosomes, while facilitating tumor progression, also present opportunities in diagnostics and targeted drug delivery by carrying specific cancer biomarkers. The beneficial impacts of stem cells are conveyed through exosomes, bypassing the disadvantages associated with the cells themselves.[22–24] Plant-derived extracellular vesicles (PDENs) carry bioactive molecules, including proteins, lipids, and RNAs, that have shown potential in modulating cellular functions. However, due to differences in receptor compatibility, PDENs do not exhibit the same level of interaction with mammalian cells as mammalian exosomes. Although PDENs are promising for applications in inflammation, immune regulation, and tissue regeneration, these effects remain limited. The current understanding of PDEN-mammalian cell interactions is largely based on in vitro studies, underscoring the need for further investigation to better assess their efficacy in mammalian systems.

Exosomes in Cosmetic Dermatology

Exosomes have garnered significant attention in the realm of cosmetic dermatology due to their remarkable potential for skin rejuvenation.[7,12,22] It is most probable that the majority of commercially available exosomes are a mixture of extracellular vesicles or a combination of apoptotic bodies, endosomes, etc. Overall, the multifaceted benefits of exosomes in skin rejuvenation are supported by a growing body of literature. Their ability to stimulate extracellular matrix production, enhance skin hydration, modulate inflammation, and support wound healing positions them as a powerful tool in cosmetic dermatology. As research continues to advance, exosome therapy holds promise for becoming a mainstream non-invasive aesthetic modality for those seeking to maintain youthful, healthy skin.[7,12]

Skin Rejuvenation

Studies have highlighted the potential of exosomes in enhancing skin health and combating the signs of aging. Research highlights their multifaceted roles, particularly in promoting collagen and elastin, which are critical for maintaining skin elasticity and firmness.[25–27] Studies indicate that exosomes derived from MSCs not only boost the production of these essential proteins but also inhibit the activity of enzymes such as matrix metalloproteinases (MMP) that degrade them, thus effectively combat signs of aging such as wrinkles and skin laxity.[28] Additionally, exosomes enhance skin hydration and barrier function. They do this by facilitating the transfer of biomolecules, including hyaluronic acid, ceramides, and various growth factors.[29] Studies, such as those by Li et al have shown that PDENs can deliver specific antioxidants like vitamin C and glutathione, as well as moisturizing factors such as hyaluronic acid and polysaccharides. These components

help reduce oxidative stress and enhance the skin's moisture content and its natural ability to retain moisture. Moreover, exosomes can strengthen the skin barrier by promoting the proliferation and differentiation of keratinocytes, leading to improved skin resilience and protection against environmental stressors.[30,31] This dual function promotes a healthier, more resilient skin surface and offers a promising non-invasive alternative to traditional skin rejuvenation techniques. The cumulative effect of these properties positions exosomes as a potential groundbreaking tool in aesthetic medicine, providing a foundation for innovative therapies that harness the body's own regenerative capabilities to achieve natural, lasting cosmetic improvements.

While several studies indicate exosomes as promising agents in treating aged skin, skin augmentation utilizing conditioned media, particularly from fibroblast cultures, has shown potential benefits. These media are known to contain a variety of bioactive molecules that contribute to skin health. Studies, such as those by Mehta et al, highlight their capacity to enhance collagen and elastin synthesis, reducing wrinkle depth and improving skin resilience.[32] Although traditionally believed to include exosomes, it is essential to note that further research is needed to confirm their exact composition, including whether these components indeed contain active exosomes or represent other bioactive elements.

The highest evidence for skin rejuvenation is available through platelet-derived exosomes or human platelet extract. These exosomes are known for their rich content of regenerative miRNA signaling, which can promote healing and tissue repair. Keeping the characteristics of wrinkles and their evolution in mind, a topically applied platelet-derived exosome product presents an interesting case for investigation. A study on this technology, specifically human platelet extract, demonstrated significant improvements in redness, wrinkles, and dyschromia across all cosmetic units, along with noticeable enhancements in luminosity and color evenness at 4 to 6 weeks on facial photodamage and cutaneous aging. The product was found to be safe, well-tolerated, and well-received by participants.[33–37]

Another example is a study performed by Chernoff, which establishes the enhancement that MSCs-derived exosomes caused when used as a primer before CaHA injections, yielding enhanced skin quality faster than exosomes or CaHA alone. This study testifies the optimal efficacy of exosomes in combined procedures compared to individual ones. Apart from being effective in combination with products such as CaHA, exosomes have shown auspicious results combined with different application methods as well.[38]

Similarly, in their study, Bai et al utilized an ex vivo model involving human skin explants to investigate the potential of exosomes in treating aged skin. The researchers applied exosomes derived from adipose-derived MSCs topically to the skin explants and assessed their impact on collagen synthesis, elastin production, skin hydration, and barrier function. The study found that these exosomes significantly promoted collagen synthesis and improved elastin levels, which are critical for maintaining skin elasticity and firmness. Additionally, the exosomes enhanced skin hydration by increasing hyaluronic acid levels and strengthened the skin barrier by boosting ceramide production. These effects contributed to a reduction in visible signs of aging, such as wrinkles and skin laxity, and resulted in a healthier, youthful appearance in the treated skin explants.[39] Additional insights from studies by Subha et al and Cho et al. highlight the potential of PDENs in skin regeneration. Subha et al observed that PDENs contribute to wound healing and skin regeneration due to their abundance of bioactive molecules, which help reduce oxidative stress and increase skin moisture levels. These properties may assist in preventing wrinkle formation, presenting a holistic approach to skin rejuvenation. However, despite these promising findings, such effects are predominantly observed in vitro. Cho et al conducted a comparative analysis of keratinocyte transcriptomes, suggesting that plant-derived exosomes may effectively deliver bioactive substances to the skin. Nevertheless, the effectiveness of PDENs in skin applications remains to be fully established, as in vivo human studies are essential for confirming their efficacy and safety.[40,41]

Hair Restoration

Exosomes have emerged as a new option for hair growth, particularly in addressing conditions such as androgenetic alopecia.[42] The literature supports the potential of exosomes as an effective treatment for hair growth. Their ability to deliver growth factors enhances vascularization and modulates inflammation. It makes them a versatile and promising option for individuals seeking to combat hair loss and improve hair density. As research continues to advance, exosome therapy may become a mainstream non-invasive treatment for hair restoration.[43,44]

Research indicates that exosomes derived from dermal papilla cells (DPCs) significantly enhance hair growth by stimulating the proliferation and differentiation of hair follicle cells. Studies using both in vitro cultured human hair follicles and in vivo, animal models have shown that these exosomes promote hair density and thickness by modulating key signaling pathways like Wnt/β-catenin, crucial for hair development. Additionally, DPC-derived exosomes exhibit anti-inflammatory properties that reduce scalp inflammation, creating a favorable environment for hair follicle regeneration. These findings suggest that DPC-derived exosomes could be a promising option for hair restoration, particularly in conditions where inflammation contributes to hair loss.[45–49] In a related context, platelet-rich

plasma (PRP) also contains platelet-derived exosomes, as platelets naturally release exosomes during their involvement in wound healing and tissue repair. These exosomes carry a variety of bioactive molecules, including growth factors, cytokines, and microRNAs, which influence cellular processes such as proliferation, migration, and differentiation. A study by Nilforoushzadeh et al. demonstrated that while PRP-derived exosomes (PRP-Exo) positively impact DPCs, exosomes derived from adipose-derived stem cells (ASC-Exo) were more effective in promoting DPC proliferation and migration. This suggests that ASC-Exo might offer superior cosmetic potential for enhancing hair follicle activity and could provide a new approach to treating hair loss, potentially surpassing the effects of PRP-Exo.[50]

Dyschromia

Exosomes are emerging as a promising solution for dyschromia disorders, such as melasma and solar lentigines. Research indicates that exosomes derived from plant sources or other innovative biotechnologies can inhibit melanin synthesis by downregulating the activity of melanogenic enzymes like tyrosinase. Their ability to deliver targeted molecular signals makes them effective in treating conditions such as melasma and age spots, offering a more natural and less invasive alternative to traditional skin-lightening treatments. Their ability to inhibit melanin synthesis can be leveraged to treat hyperpigmentation, providing a more even and radiant complexion. In the research conducted by Wong et al, these insights are expanded upon, demonstrating that exosomes can play a crucial role in modulating immune responses and melanogenesis, which are key factors in skin health and aesthetics. Their study specifically underscores the potential of exosomes to regulate melanin production, as observed in the context of vitiligo, an autoimmune condition characterized by the loss of pigmentation. The findings from this study highlight how exosomes can influence melanocyte activity and immune responses, thereby offering cosmetic avenues for treating hyperpigmentation disorders by inhibiting melanin synthesis, which can help achieve a more even and radiant complexion.[51] Another study conducted by Kim et al investigates the regulatory effects of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) on melanogenesis. Their findings suggest that this conditioned medium can significantly inhibit melanin production, which has implications for treatments aimed at reducing hyperpigmentation. Melanogenesis is primarily regulated by the microphthalmia-associated transcription factor (MITF). MITF drives the expression of key enzymes involved in melanin production. The research demonstrated that hUCB-MSCs lead to the proteasomal degradation of MITF. By decreasing the stability and levels of MITF, the stem cell-derived factors effectively reduce melanin production in melanocytes responsible for melanin synthesis.[52] Cho et al explored the skin-brightening effects of exosomes derived from human ADSCs through a prospective, split-face, randomized, placebo-controlled trial. The participants in the study had hyperpigmentation issues, such as uneven skin tone and dark spots. The exosomes were delivered topically to the participants' skin, specifically targeting these pigmentation irregularities. The study aimed to evaluate the effectiveness of the exosome treatment in improving skin brightness and overall complexion compared to placebo treatments. Their findings revealed that exosomes could significantly enhance skin brightness compared to placebo treatments. Their study demonstrated that exosomes act by modulating key signaling pathways involved in melanin synthesis and distribution, thereby reducing hyperpigmentation and promoting a more even skin tone. This effect was quantitatively measured using standard dermatological assessments, including spectrophotometric measurements of skin brightness, which showed a clear improvement in skin tone and brightness on the treated side of the face compared to the placebo side. Additionally, clinical evaluations by dermatologists and self-assessment questionnaires completed by participants further supported these findings, noting a reduction in dark spots and an overall more even skin tone. This promising result underscores the potential of exosomes as an innovative aesthetic approach in cosmetic dermatology for achieving an effective treatment for hyperpigmentation.[41]

Safety and Complications

Exosomes have shown considerable promise in cosmetic dermatology, but several safety concerns and potential complications need to be addressed. Although exosomes are generally considered biocompatible, their long-term safety profiles are not fully understood. Exosome-based therapies vary in immunogenicity and scalability depending on whether they are autologous or allogeneic, and whether they are derived from single or pooled donor MSC or platelet sources. Autologous exosomes, sourced from the patient's own cells, typically pose minimal immune risks but are less scalable. In contrast, allogeneic exosomes, derived from donor cells, offer greater scalability but carry higher immunogenicity risks if it is MSC-based. Single donor exosomes provide consistency but are limited in supply, while pooled donor exosomes increase availability but introduce variability and potential immune responses. These factors necessitate rigorous quality control and monitoring to ensure the safety and efficacy of exosome therapies.

Some studies have reported mild to moderate complications, such as redness, swelling, and irritation at the injection site, which are typically transient.[53,54] Therefore, more research is required before exosomes can be fully and safely applied in the field of cosmetic dermatology. Additionally, the source of the exosomes raises safety concerns regarding infection risk; if exosomes are not properly purified or tested for pathogens, they can increase the risk of infection. There is also concern that exosomes derived from cancerous cells could promote

tumor growth or metastasis.[20] The variability in the sources of exosomes , whether from adult stem cells, fetal stem cells, fibroblasts, plant-derived, or platelets and the method used to isolate them lead to inconsistent quality and efficacy.[55] This variability complicates quality control and manufacturing, resulting in a lack of standardized protocols and variations in the bioactivity and safety of exosome preparations. Lastly, there is lack of long-term data on the safety and efficacy of exosome-based therapies, which further underscores the need for extensive research before these therapies can be widely adopted.[56]

Limitations

Despite the promising potential of exosomes in cosmetic dermatology, several limitations must be addressed to advance their application in clinical settings. A significant limitation is the heavy reliance on in vitro and animal model studies, which, while providing valuable preliminary insights, are insufficient to confirm the efficacy and safety of exosomes in human applications. This gap emphasizes the need for extensive clinical trials that can offer robust and reliable data on the potential of exosomes in humans. Additionally, the isolation and characterization of exosomes vary widely across studies, leading to inconsistent results and complicating efforts to standardize protocols. This variability can significantly affect the reproducibility of results, making it challenging to draw definitive conclusions. Moreover, the small sample sizes in existing clinical studies further limit the generalizability of findings, making it difficult to apply these results to broader populations. Another critical limitation is the heterogeneity in exosome sources and preparation methods. The differences in sourcing exosomes, from stem cells, platelets, or plant cells, and the methods used to isolate them lead to inconsistent quality and efficacy. This variability necessitates the development of standardized protocols to ensure consistency in exosome-based treatments.

Furthermore, the lack of long-term data on the safety and efficacy of exosome-based therapies poses another significant challenge. Without long-term studies, it is difficult to assess the risks of chronic inflammation or other delayed adverse effects that might arise from exosome treatments. Lastly, the scalability and cost-effectiveness of exosome production remain significant hurdles for widespread clinical adoption. Developing standardized manufacturing processes that can produce high-quality exosomes consistently and at scale is essential for making these therapies accessible and reliable. Due to these factors, the regulatory environment is complex and still evolving, with a pressing need for clear guidelines to standardize exosome-based treatments and mitigate potential risks. Overall, while preliminary findings are encouraging, thorough investigation into the safety and standardization of exosome therapies is crucial for their reliable and widespread use in cosmetic dermatology. Addressing these methodological, safety, and regulatory challenges is crucial for advancing the use of exosomes in cosmetic dermatology.

Future Directions and Regulatory Landscape

Exosome-based therapies represent a rapidly advancing field with significant potential in clinical applications, particularly in cosmetic dermatology. However, the commercialization and widespread adoption of these therapies face substantial regulatory challenges. In the US, the FDA has not yet approved any exosome-based products for injection due to concerns over safety, efficacy, and the lack of standardized production processes. The regulatory landscape is similarly stringent in the European Union, where human-derived exosomes face tight restrictions, driving interest in plant-based exosome alternatives that may offer a safer and more acceptable option for cosmetic application. PDENs are gaining traction as they bypass many of the regulatory issues associated with human exosomes, contributing to their growing popularity and consumer demand. Yet, their true utility for mammalian cell interaction remains in question.

Globally, the regulatory approach to exosomes varies significantly. In 2019, the FDA issued cautionary notes regarding the use of exosomes but has yet to establish comprehensive guidelines for their production and use. Currently, exosomes are classified under the drug category, requiring additional regulations for premarket review, which complicates the development of clear guidelines in the US. In contrast, the European Medicines Agency (EMA) does not automatically classify exosomes as drugs. Instead, exosomes are considered advanced medicinal products, particularly when they contain functionally translated RNA intended for aesthetic enhancement purposes. The Committee for advanced therapies at EMA categorizes exosomes with functional RNA as gene therapies.[8] In Asia, Japan regulates exosome-based products under its regenerative medicine framework, with the Ministry of Health, Labour, and Welfare and the Pharmaceuticals and Medical Devices Agency classifying these products as biologics. This classification necessitates stringent regulatory oversight, including rigorous quality control, clinical trials, and marketing authorization. South Korea, through the Ministry of Food and Drug Safety, also classifies exosomes as biologics, adhering to standards similar to those of the International Society for Extracellular Vesicles (ISEV). Despite the lack of approved exosome products, South Korea is advancing rapidly in the aesthetic applications of exosomes. Taiwan's regulatory approach falls under the Regenerative Medicine Development Act, incorporating international standards for safety and efficacy. Taiwan's Center for Drug Evaluation (CDE) has also drafted guidelines for exosome-based product manufacturing and is expanding its role in the global market through its Contract Development and Manufacturing Organization industry.[9]

To advance the field of exosome-based therapies in cosmetic dermatology, it is crucial to address these regulatory challenges by developing standardized protocols for the isolation and characterization of exosomes, which are essential for ensuring consistent and reproducible results. Additionally, conducting large-scale, randomized controlled trials is necessary to validate preclinical findings and establish the efficacy and safety of exosome-based treatments in humans. Exploring the potential of combining exosomes with other procedural modalities, such as laser therapies, could enhance their efficacy and provide synergistic effects, ultimately leading to more effective, safe, and widely accessible treatments in aesthetic medicine. All of these potentials require meticulous regulatory guidelines, currently lacking in this field.

CONCLUSION

Owing to their high potential in treating dermatological conditions individually, exosomes' flexibility to fit in various types of procedures adds to their value in cosmetic dermatology. When paired with other dermatological procedures such as laser treatments, exosomes may support healing, reduce inflammation, and improve skin structure post-treatment, optimizing rejuvenation effects and potentially reducing recovery times. Consequently, despite limited clinical evidence, the efficacy of exosomes in aesthetics and cosmetic dermatology, particularly in skin rejuvenation and hair growth, is imaginable. However, significant challenges remain, including the need for standardized isolation methods, extensive clinical trials, and a better understanding of their long-term safety. Although the US, EU, Japan, Taiwan and South Korea have not published any official guidelines for the use of exosomes on broad scales, they are on the path to establishing them. Addressing these challenges through future research and regulatory efforts will be crucial for fully leveraging the benefits of exosomes in this field.

DISCLOSURES

DH, LG, and HC declare no conflicts of interest. MG acts as a consultant and has performed clinical research for ExoCoBio/Benev. Additionally, he consults with Rion Aesthetics and AnteAGE. SW acts as a consultant for Rion Aesthetics.

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Dermatoporosis and the March of Time: Advances in Understanding and Managing Chronic Progressive Cutaneous Fragility in Aging Skin

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Abstract

Dermatoporosis refers to a skin condition affecting the elderly, characterized by chronic progressive cutaneous insufficiency and skin fragility. Primary dermatoporosis is due to chronological skin aging, genetic factors, and environmental damage while secondary dermatoporosis is caused by chronic exposure to topical and systemic corticosteroids. Dermatoporosis may initially be seen as a cosmetic problem, but serious complications such as skin tears and deep dissecting hematomas can occur as skin fragility increases. The pathophysiologic mechanisms of dermatoporosis suggest several interventions with the potential to slow progression and reduce the risk of skin tearing. Therefore, recognizing early signs and promptly initiating treatment may help to manage the condition and reduce the risk of complications. Treatment and prevention may include sun protection, emollients, and long-term use of topical retinoids as they promote improved skin quality. Other available treatments include the application of matrikines and α-hydroxy acids, such as mandelic acid. Proper skin care can also preserve skin quality and integrity and enhance skin elasticity and smoothness by using products formulated with ingredients that target skin atrophy, dryness, and elasticity. A commercial product has applied a novel proprietary technology to create a moisturizing lotion containing Centella asiatica and mandelic acid to create a clinically effective product for dermatoporosis-prone skin (Cetaphil® Skin Care; Galderma Laboratories, LP). This product is formulated with a pH range of 4-5 to help reduce elevated pH of aged skin, improving physiological skin function, and promoting overall skin health. Maintaining the normally acidic skin pH supports normal microbial colonization and prevents the growth of pathogenic bacteria.

Introduction

Dermatoporosis is a term applied to a prevalent skin condition affecting the elderly[1] and is used to describe the many features of chronic cutaneous fragility syndrome. This name was chosen to convey a concept analogous to the age-related condition osteoporosis.[1] Primary dermatoporosis is due to endogenous or chronological skin aging, genetic factors, and exogenous factors, such as smoking and long-term exposure to solar radiation.[2] Secondary dermatoporosis is caused by some medications, such as corticosteroids and anticoagulants.[3] In primary dermatoporosis, direct damage to cells and extracellular matrix (ECM) leads to senescence and progressively thinning skin. In secondary dermatoporosis, drug interference with cell function and replication leads to an insufficient ECM environment, which leads to senescence and progressively thinning skin. Other factors that may contribute to dermatoporosis include menopause,[4] diabetes, renal failure,[5] and a sedentary lifestyle.[6] Untreated dermatoporosis can lead to severe skin damage.[3,7]

Dermatoporosis is not an uncommon condition. In 2 European studies, the prevalence of dermatoporosis was 30.7% and 32% to 37% among individuals >60 through 65 years old.[5,8] In the United States, the prevalence is likely to grow due to the aging "baby boomer" population.[9] An observational study assessed patients with a mean (SD) age of 72.6 (7.8) years (range, 60-95 years) for the prevalence and comorbidities associated with dermatoporosis (N=370).[10] The median age of patients with dermatoporosis was significantly older (77 vs 71 years, *P*<0.0001). There was a greater prevalence among men (24% vs 9%) with most being Stage 1 (8%) (Table 1).[10]

Table 1. Stages of Dermatoporosis

Stage I	Skin atrophy, senile purpura, and pseudo-cicatrices
Stage IIa	Localized and small superficial lacerations (<3 cm) due to skin fragility
Stage IIb	Larger lacerations (>3 cm)
Stage IIIa	Superficial hematomas
Stage IIIb	Deep dissecting hematomas without skin necrosis
Stage IV	Large areas of skin necrosis with potentially lethal complications

From Saurat et al, 2017.[73]

Pathogenesis

The dermis is mainly comprised of the extracellular matrix. It principally consists of hyaluronic acid, a glycosaminoglycan produced by fibroblasts, proteins, and glycoproteins. The ECM provides physical support, maintains skin hydration, and elasticity, acts as a protective barrier, and supports cell structure and vasculature.[11,12]

The amount of hyaluronic acid in the dermis decreases with age, causing the skin to atrophy and become susceptible to trauma.[12] Hyaluronic acid is also responsible for the proliferation of keratinocytes via interactions with the CD44 cell surface receptor.[7] Diminished CD44 expression is correlated with skin atrophy and may result from the decreased presence of hyaluronic acid and exposure to aggravating conditions, such as corticosteroids and ultraviolet light. As described below, CD44 may be a target for some dermatoporosis treatments.

A strong skin barrier requires a robust ECM maintained by fibroblasts and keratinocytes. Keratinocytes are an essential part of barrier protection against environmental insults. They maintain a basal population, undergo cornification, excrete intracellular components, and continuously turn over, ensuring constant regeneration of the skin barrier.[13] Fibroblasts are crucial for maintaining skin integrity and responding to skin damage and inflammation. Fibroblasts are also found in the dermis layer, producing materials for the ECM, such as collagen, elastin, and glycosaminoglycan, which also contributes to skin bulk, strength, and resilience.[14,15] They support ECM production, regulate the intracellular environment and help maintain stem cell populations.[16,17]

A newly described organelle called the hyaluronosome produces hyaluronic acid and contains CD44 and heparin-binding epidermal growth factor.[18] This organelle may be functionally deficient in patients with dermatoporosis.

Finally, up-regulation of matrix metalloproteinases (MMPs), particularly collagenase-1 (MMP-1), stromelysin-1 (MMP-3), and gelatinase A (MMP-2) occurs in aging skin, causing the breakdown of collagen and elastin during chronological skin aging.[19] Conversely, the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) decreases with fibroblast senescence. It is via MMP activation that ultraviolet light causes photodamage to the skin.[20]

Diagnosis

Dermatoporosis is similar to other skin disorders that also result in aging skin frailty and damage caused by excessive exposure to ultraviolet A and B radiation.[21,22] The differential diagnosis includes actinic purpura, also known as solar purpura or senile purpura, characterized by dark purple macules and extensive ecchymosis,[21] and dermatoheliosis, or photoaging characterized by irregular pigmentation, lentigines, and hyperpigmentation.[22] It is most common among individuals with Fitzpatrick skin phototypes I through III. In contrast to skin disorders directly driven by ultraviolet damage, dermatoporosis is primarily due to senescence[23] and characterized by skin atrophy, purpura, pseudo scars, and skin lacerations.[3,7]

Complications

Deep dissecting hematomas are a major late-stage complication of dermatoporosis.[24] Dissecting hematomas are rapidly expanding collections of blood that split the hypodermis from the muscle fascia.[25] These may occur following minor skin trauma[25] and most commonly among older women with a mean age of 82 years in one report.[26] In one series, patients initially developed erythema and edema, progressing to skin necrosis. Hospital treatment consisted of deep incision and debridement, wound closure, and skin grafting or other standard wound care. The mean length of hospitalization was 3.5 weeks.[26]

Skin tears are another potential complication of dermatoporosis. Among subjects evaluated in one study (*N*=128), 6 (4.6%) had skin tears.[24] The frequency of prior skin tears was 19.5%.[27] Delayed wound healing is another complication in this patient population,[28] especially on the lower extremities below the knee.[7] This effect on wound healing is likely due to diminished keratinocytes and fibroblasts and overexpression of matrix metalloproteinases.

In one observational study, complications (32%) included skin lacerations (Stage 2a, 30%) and 1 patient with superficial hematomas (Stage 3a). Multivariate analysis revealed a significant association with high-potency topical corticosteroids (P=0.002), oral corticosteroids (P=0.022), anticoagulant therapy, chronic renal failure (P=0.013), and age (P=0.016).[5]

Treatments for Dermatoporosis

Understanding the early signs of dermatoporosis and promptly initiating treatment may halt disease progression and reduce the risk of complications.[28]

Retinoids

A common treatment for thinning skin conditions, including dermatoporosis, is the application of topical retinoids as they promote keratinocyte proliferation and collagen synthesis to improve the epidermal barrier, inhibit collagen degradation, and reduce transdermal water loss and metalloproteinase activity.[2,29] Retinoids can also increase hyaluronic acid synthesis and CD44 expression.[30,31] In this way, retinoids reduce the clinical signs of photoaged skin.[32-34] Retinoids include retinol (vitamin A) and related compounds such as retinoic acid, retinaldehyde, retinyl palmitate, tretinoin, and others.[29] Tretinoin improves facial wrinkling, hyperpigmentation, and skin texture[29] and is considered the gold standard for skin rejuvenation.[35] The ability of once-daily application of tretinoin 0.025% to 0.01% cream to improve the appearance of photodamaged skin has been demonstrated in large double-blind studies.[36,3738]

Matrikines

Peptides, known as matrikines, have been identified and are involved in numerous skin conditions, including skin aging.[39] Matrikines are formed by the proteolysis of ECM macromolecules, which have the ability to regulate cell activities, including cell proliferation, migration, protease production, and apoptosis.[40,41] Peptides with beneficial matrikine-like effects on aging skin include glycine-histidine-lysine tripeptide, glycine-glutamate-lysine-glycine tetrapeptide (GEKG), lysine-threonine-threonine-lysine-serine pentapeptide, and carnosine[35,40,42] Several in vitro and in vivo studies have demonstrated the topical application of the matrikine GEKG stimulates ECM protein expression of collagen, hyaluronan, and fibronectin, which was associated with significant improvement in the physiological and clinical appearance of aging skin.[43]

One clinical trial assessed the efficacy of a peptide-containing formulation on facial wrinkles and skin laxity.[44] Adult photoaged women treated for 6 months achieved significant improvement in undereye wrinkles starting at 1 month of treatment. After 6 months, 82% of treated participants showed improvement. Similarly, lateral canthal lines showed improvement beginning after 2 months of treatment, and by 6 months, 71% of participants showed improvement. A significant improvement in skin firmness was achieved after 1 month, and at 6 months, 97% of participants showed improvement.

α-Hydroxy Acids

These compounds are widely found in cosmetic products used to address aging skin.[45] It has been suggested that α-hydroxy acids owe their beneficial effects to their ability to chelate calcium ions in the epidermis, causing desquamation and promoting new skin growth.[46] When applied to the forearm, glycolic, lactic, or citric acid-containing lotions produced ~25% increase in skin thickness associated with increased mucopolysaccharides, improved elastic fiber quality, and increased collagen density.[47] Similarly, the application of citric acid lotion for several months also increased epidermal thickness and dermal glycosaminoglycans in treated skin.[48] Topical mandelic acid can also exfoliate the skin to reduce hyperpigmentation and promote collagen production.[49]

Other Therapies

Numerous other therapies have been reported to have beneficial effects on aging skin and dermatoporosis. One 6-week study demonstrated the daily application of human epidermal growth factor to skin affected with senile purpura lesions decreased the number of purpuric lesions and increased mean skin thickness, thereby reducing psychological distress and preventing the advancement of dermatoporosis.[50] The effect of the steroid hormone dehydroepiandrosterone (DHEA) on aging skin has also been assessed.[51] When topically applied to the face and hands for 4 months, DHEA improved skin brightness and improved the appearance of atrophic skin.

Vitamins can also play an important role in the cause and treatment of dermatoporosis. It has been speculated that symptoms of dermatoporosis may arise from vitamin C deficiency[52], and a 12-week randomized, double-blind study assessed the efficacy of twice-daily application of topical 5% vitamin C for treating Bateman purpura.[53] The result was clinical improvement of purpura as well as beneficial effects on skin elasticity and thickness. Similarly, vitamin D and vitamin A have preventative and therapeutic effects for aging skin.[54-56]

Prevention

The obvious first steps in preventing the occurrence of dermatoporosis are avoiding known causes of the condition, such as ultraviolet radiation exposure and smoking, and limiting the use of some medications, such as corticosteroids, whenever possible.[7] Practicing proper skin care is also important to protect the skin and maintain normal skin hydration, as well as to support a healthy skin barrier. Proper skin care can preserve skin quality and integrity and enhance elasticity and smoothness.[57,58] It is also important to become aware of the early signs of dermatoporosis so that early treatment can be initiated to halt disease progression (staging) and maintain a patient's quality of life.[59,60] Current evidence indicates proper skin hygiene and the use of emollients have preventative benefit for aging patients in the hospital and residential care settings.[61]

Achieving proper skin care requires the use of products formulated with ingredients that target skin atrophy, dryness, and elasticity. Skin atrophy can be reduced with ingredients that increase collagen production,[62-64] promote cell turnover,[63] and stimulate cellular proliferation.[64] Skin dryness can be minimized with ingredients that improve skin moisture by increasing skin surface hydration and decreasing transepidermal water loss,[62,63] which improves skin barrier function,[62] and exfoliation, which allows better penetration of beneficial ingredients into skin.[49,63] Skin elasticity can be improved with ingredients that increase elastic fibers[65] and collagen production.[62-64]

The accumulation of senescent cells in the epidermis increases with age and has a negative effect on tissue. Senescent cells are associated with fibroblast dysfunction, inflammatory cytokine production, breakdown of the ECM, and weakening of the dermo-epidermal junction.[66] Senescent cells in the epidermis are preferentially removed through JAG1-NOTCH1 signaling in the epidermis[67]; however, this mechanism declines with advancing age. It has been shown that the addition of combined microdoses of *Centella asiatica* (0.005%) and mandelic acid (0.05%) to cultured human keratinocytes and fibroblasts resulted in a significant decrease in senescent cells with associated cell toxicity.[66]

The importance of skin pH for maintaining normal skin barrier function has long been recognized.[68] The skin normally has an acid pH ranging from 4 to 6. Advancing age is associated with increasing skin pH and diminished barrier function.[69] Consequently, it is also important to regularly apply a product

with a pH range of 4-5 to help reduce elevated pH levels in aged skin, improving physiological skin function and promoting overall skin health.[70] Aged skin often has an increased surface pH of ~6, needing appropriate skin care to counterbalance this increase and improve barrier function.[70,71] Maintaining the normally acidic skin pH supports normal microbial colonization, providing optimal growth conditions for commensal microorganisms.[72] Pathogenic bacteria, such as *Staphylococcus aureus*, thrive in neutral pH conditions (eg, pH 7.5), but growth is reduced under acidic conditions.[72] Thus, increased skin pH disrupts the microbiome balance, promoting pathogenic colonization and increasing susceptibility to infections.[72] The distribution of skin lipids is also dependent on pH-regulated mechanisms, as increased skin pH can lead to defective lipid processing and delayed maturation.[72] The enzymes responsible for generating ceramides exhibit reduced activity at higher pH levels, impairing the protective skin barrier.[69,72]

Conclusion

Dermatoporosis is a common condition among the elderly with potentially far-ranging consequences. While there are several treatments available to treat dermatoporosis, greater emphasis should be placed on routine preventative measures. This includes the regular use of topical products formulated to promote collagen synthesis, stimulate dormant fibroblasts, decrease hyaluronic acid degradation, enhance keratinocyte proliferation, and maintain normal skin pH to support normal microbial colonization.

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For additional education on this topic, please see “Novel Strategy for Strengthening Dermatoporotic Skin by Managing Cellular Senescence” at https://jddonline.com/articles/novel-strategy-strengthening-dermatoporotic-skin-managing-cellular-senescence-S1545961624P8388X.

Disclosures

GA serves has served as a research investigator for Galderma.

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ORIGINAL ARTICLE

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Gender, Racial, and Fitzpatrick Skin Type Representation in Melasma Clinical Trials

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ABSTRACT

Melasma, a symmetric pigmentary disorder, is more prevalent in women and individuals with darker skin tones. Despite its global prevalence, there is a notable gap in the understanding of gender, racial, and Fitzpatrick skin type (FST) representation in melasma clinical trials. We conducted a comprehensive search of the United States (US) National Library of Medicine clinical trials database (ClinicalTrials.gov) on March 2nd, 2024, to identify melasma clinical trials. The aim of this study was to assess the demographic representation of participants enrolled in melasma clinical trials. Out of 56 trials identified, 19 met the inclusion criteria, comprising 614 patients. Our analysis revealed a predominant representation of female patients (96.58%) and a diverse representation of racial and ethnic groups, with a majority of Hispanic or Latino patients (43.10%), followed by Asian (23.71%), White (15.52%), and Black or African American patients (14.66%). Fitzpatrick skin types III and IV were most common among trial participants, totaling over 75% of trial participants. The identified gender, racial, and FST representation suggest a deliberate effort towards more inclusive research practices in dermatology. This trend towards inclusivity sets a valuable precedent for improving representation in research for other dermatological conditions that disproportionately impact skin of color patients.

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INTRODUCTION

Melasma, a symmetric pigmentary disorder, develops primarily on the face.[1] Melasma typically presents as light brown to dark brown macules and patches on the forehead, malar region, and chin.[1] Melasma is more prevalent in women and individuals with darker skin tones.[1] Melasma is attributed to multiple etiologies, including ultraviolet (UV) sun exposure, hormonal influences, pregnancy, cosmetics, birth control, and antiseizure or phototoxic drugs.[1-3] Although the precise age of onset varies, melasma generally occurs between 20 to 30 years of age.[3] The global prevalence worldwide is estimated to be around 1%, while in higher-risk populations, the prevalence has been found to range from 9% to 50%.[2] Melasma not only leads to considerable psychological and emotional distress but also significantly affects a patient's quality of life.[4,5] This impact is particularly pronounced in patients with skin of color, who experience a higher frequency of melasma and greater associated morbidity.[4,5]

The prevalence of melasma varies by race, and existing data on melasma prevalence is often limited to the demographics of specific locations where studies are performed. The prevalence of melasma in Latino populations ranges from 8.2% to 8.8%, while an Arab-American population in Michigan showed a 15.5% prevalence rate.[6,7,8] In contrast, the prevalence of melasma was found to be 4% in a black population in Durban, South Africa.[9] The prevalence of melasma was found to be 2.9% in Saudi Arabia and 1.5% in Ethiopia.[10,11] The prevalence in India is as high as 41.1%.[12] Asian countries such as Nepal and China also report prevalence rates of 6.8% and 13.6%, respectively.[13,14]

As the demographic landscape of the United States continues to diversify, with one in three Americans projected to be a race other than White by 2060, the need for inclusivity in dermatologic research becomes increasingly necessary.[15] Racial minorities are often underrepresented in dermatology clinical trials, including trials involving hidradenitis suppurativa (HS), nail psoriasis, psoriatic arthritis, and laser treatments for scars.[16-20] There is currently a gap in knowledge pertaining to patient representation in melasma clinical trials. Given the documented underrepresentation of skin of color participants in dermatologic clinical trials and the higher prevalence of melasma within these populations, we aim to analyze gender, racial, and Fitzpatrick skin type (FST) representation in melasma clinical trials.[16-20]

MATERIALS AND METHODS

The US National Library of Medicine clinical trials database (ClinicalTrials.gov), an international registry of clinical trials, was searched on March 2nd, 2024, to identify melasma clinical trials. We searched the term "melasma" and filtered for "completed" status. For trials that did not report their results on ClinicalTrials.gov, we searched for the corresponding publication. Trials that did not provide gender, racial, or Fitzpatrick skin type data were excluded. Similar methods have been used in other publications analyzing racial and ethnic representation in HS clinical trials.[19] The following information was obtained: title, year, total number of participants, gender, race or Hispanic origin, and FST. Calculations for race or Hispanic origin and FST percentages were made using only the trials that reported this specific data.

RESULTS

A total of 56 trials were identified on ClinicalTrials.gov. After removing all studies that did not include gender, racial or Hispanic origin, or FST data, 19 trials remained (total of 614 patients). Out of the included clinical trials, 19 trials reported gender data, 9 included race or Hispanic origin data, and 15 included FST data. Female patients comprised the majority of participants (96.58%; Figure 1). Hispanic or Latino patients comprised 43.10% of trial participants, followed by Asian (23.71%), White (15.52%), and Black or African American patients (14.66%; Table 1). There were no American Indian or Alaska Native and Native Hawaiian or Pacific Islander participants in any of the included clinical trials. In contrast, the demographic composition of the United States according to the 2023 census data was 75.5% White, 19.1% Hispanic/Latino, 13.6% Black, 6.3% Asian, 3.0% Native Hawaiian or Pacific Islander, and 1.3% American Indian or Alaska Native (Figure 2).[21]

FIGURE 1. Gender representation in Melasma Clinical Trials compared to National Gender Distribution.

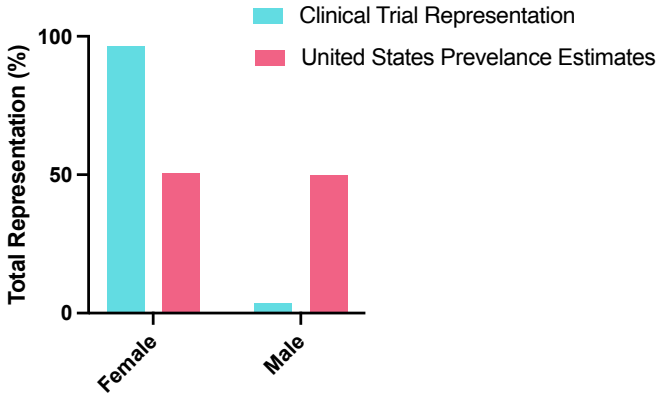
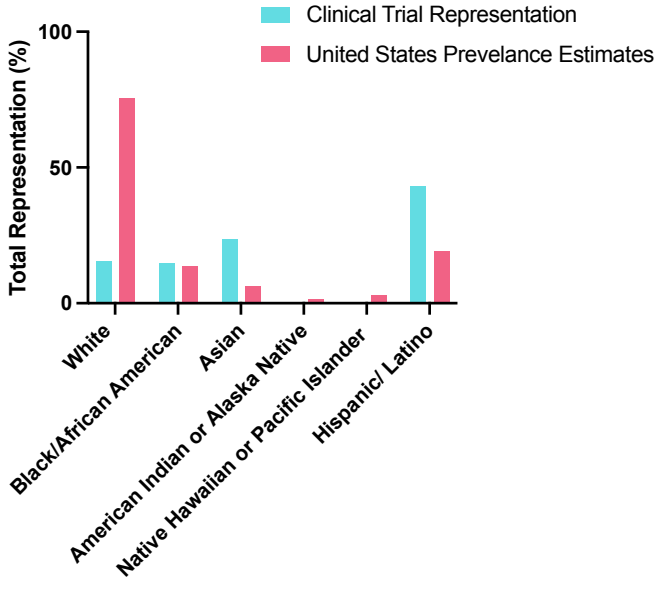


TABLE 1.

Comparison of Representation of Gender, Racial, and Fitzpatrick Skin Type in Melasma Clinical Trials Compared to National Census Demographic Data

Demographic or Parameter	Number of Study Participants, *n*	Representation in Clinical Trials, *n* (%)	Prevalence from the 2023 US Census[21], (%)
Gender	614		
Female	--	593 (96.58%)	50.4%
Male	--	21 (3.42%)	49.6%
Race and Hispanic Origin	232		
White	--	36 (15.52%)	75.5%
Black/African American	--	34 (14.66%)	13.6%
Asian	--	55 (23.71%)	6.3%
American Indian or Alaska Native	--	0 (0.00%)	1.3%
Native Hawaiian or Pacific Islander	--	0 (0.00%)	3.0%
Hispanic/ Latino	--	100 (43.10%)	19.1%
Other	--	3 (1.29%)	--
Unknown	--	4 (1.72%)	--
Fitzpatrick Skin Type	545		
I	--	0 (0.00%)	--
II	--	45 (8.26%)	--
III	--	164 (30.09%)	--
IV	--	250 (45.87%)	--
V	--	84 (15.41%)	--
VI	--	2 (0.37%)	--
VI	--		--

FIGURE 2. Racial and Hispanic origin representation in Melasma Clinical Trials compared with National Race and Hispanic Origin Distribution.



Out of the studies that included Fitzpatrick skin type data, 8.26% were type II, 30.09% were type III, 45.87% were type IV, 15.41% were type V, and 0.37% were type VI. None of the participants in the clinical trials was FST I.

DISCUSSION

To our knowledge, this is the first study to analyze gender, racial, and Fitzpatrick skin type representation in melasma clinical trials. Firstly, our data reveals a low representation of male participants in melasma clinical trials, aligning with the broader observation of melasma being less prevalent in males.[22] Previous research has identified a trend of predominant female representation in dermatology clinical trials, with women constituting 54.9% of participants, a figure significantly lower than the 96.58% observed in the current study.[23] The clinical trials identified in this study appropriately emphasize female representation as melasma is a female-predominant disorder.[22] Nonetheless, it may be beneficial to have male representation in clinical trials, as the prevalence of melasma in males varies across studies.[24-27] Brazil has a prevalence of melasma ranging from 2.5% to 6.0% in men.[24,25] The prevalence of melasma in India has been found to range from 26% to 32% in men.[26,27] It is important for men to be included in clinical trials as melasma has an equally negative impact on the quality of life for men as it does for women.[22] Melasma may also be underdiagnosed in men, as they are less likely to seek treatment compared to women.[28]

The current study revealed a higher proportion of Hispanic/Latino and Asian patients and a lower proportion of White patients in melasma clinical trials, likely reflecting the known higher prevalence of melasma among these populations.[1] This contrasts with trends observed in other dermatologic studies, which typically report a predominance of White participants and an underrepresentation of Hispanic/Latino and Black/African American populations.[16-19] When compared to the latest US census, Black/African Americans were found to be the most underrepresented racial group across all dermatology clinical trials, including psoriasis, eczema, non-melanoma skin cancer, melanoma, aesthetics, and rosacea trials.[16] Similarly, skin of color patients are underrepresented in clinical trials for HS, psoriatic arthritis, and nail psoriasis.[17-19] Similar to melasma, HS is more common in skin of color, yet this population is underrepresented in HS clinical trials.[19] Further studies regarding HS may be necessary to accurately reflect a more diverse patient population.

Given the variability in melasma prevalence across different races and geographical regions, directly comparing clinical trial representation to true prevalence rates proves challenging. Instead, we compared clinical trial representation to US Census data. While this comparison has its limitations due to the inclusion of non-US clinical trials, it may offer a valuable point of reference for determining suitable representation levels. The increased inclusion of Black/African American, Asian, and Hispanic/Latino patients in melasma clinical trials compared to US census data possibly reflects a targeted effort to recruit populations traditionally affected by melasma, with some studies even specifying Hispanic/Latino ethnicity as an inclusion criterion for enrollment.[29,30] We advocate for this practice of including a sample population that is most representative of the larger population impacted by the disease of interest to maximize a study's external validity.

The majority of melasma clinical trial participants were found to have FST III and IV, mirroring the condition's prevalence in this population.[31] In a study with 302 melasma patients in Brazil, 34% of patients had FST III, 38% had FST IV and 16% had FST V.[32] Similarly, a study in Tunisia consisting of 188 melasma patients demonstrated that 14% of patients had FST III, 45% had FST IV, and 40% had FST V.[33] Another study in Brazil with 953 melasma patients showed a distribution of 13% patients with FST II, 36% with FST III, 40% with FST IV and 10% with FST V.[24] These findings suggest that the representation of FSTs in melasma clinical trials closely mirrors the condition's prevalence in different skin types. However, it should be noted that FST does not necessarily correlate to race.[34] For example, an East Asian woman may be clinically identified as an FST type II, but Asian skin is generally considered to be non-White. This distinction highlights the need for nuanced approaches that consider both diversity of skin type and race in clinical trials.

A lack of diversity in clinical trial participation can significantly impede our understanding of the effectiveness, safety, and potential side effects of melasma treatments across different

demographic groups.[35] For instance, the response to treatment and the incidence of side effects may vary significantly between different skin types and racial backgrounds.[36] One randomized clinical trial on LED red light therapy showed that adverse events, including dyspigmentation and blistering, vary significantly based on skin pigmentation and race, with individuals of color exhibiting a lower tolerance to treatment.[36] Approaches to treatment must also be tailored; for instance, sunscreen, a critical aspect of melasma management, is frequently underutilized and perceived as unnecessary by skin of color patients.[37,38]

A strength of this study is that we analyzed all melasma-related clinical trials on ClinicalTrials.gov. A limitation of the study is that due to a lack of race and ethnicity data in melasma literature, we were unable to compare race and ethnic representation to prevalence rates of melasma. Another limitation is inconsistent reporting of demographic data, with some studies providing only FSTs or only racial and Hispanic origin information, but not both. Standardization of these parameters would be useful. Hispanic classification also varied between studies, with some including it under race and others under ethnicity. In our study, we grouped Hispanic with race, aligning with the US Census category of "race and Hispanic origin" to maintain consistency. Additionally, accurately categorizing gender and race may be challenging, as these classifications may not always clearly fit all individuals.

This study demonstrates that women, Hispanic/Latino and Asian patients, and individuals with Fitzpatrick skin types III and IV are predominantly represented in melasma clinical trials. These findings are particularly relevant, considering the higher prevalence of melasma within these groups. This diverse inclusion may be due to increased awareness and effort by researchers to include populations commonly impacted with melasma, reflecting a positive shift towards inclusivity in dermatological research. Other dermatologic conditions predominantly impacting skin of color patients should adopt similarly inclusive approaches to patient representation as that seen in melasma clinical studies.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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Acetyl Dipeptide-31 Amide: A Novel Cosmetic Anti-Inflammatory Peptide That Demonstrates Anti-Aging, Firming, and Lifting Benefits

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ABSTRACT

Background: There is continuous demand for safe, effective cosmetic ingredients to treat the signs of aging skin, including fine lines, wrinkles, brown spots, discoloration, laxity, and sagging. While there are a plethora of cosmeceutical peptides, few combine anti-aging and anti-inflammatory benefits with small size.

Methods: Preclinical and clinical studies evaluated the anti-inflammatory properties, anti-aging benefits, and tolerability of acetyl dipeptide-31 amide (AP31), a novel, small, anti-aging micropeptide, to understand its impact as a multifaceted, cosmetic, anti-aging, and anti-inflammaging ingredient.

Results: In vitro, AP31 statistically significantly reduced the release of inflammatory mediators interleukin (IL)-4, IL-6, IL-8, IL-17, and tumor necrosis factor alpha, and statistically significantly increased levels of dermal extracellular matrix components, ie, procollagen, elastin, decorin, fibronectin, and hyaluronic acid (all $P<0.05$ vs vehicle controls). Statistically significant increases in extracellular matrix biomarker levels were also seen in AP31-treated human skin explants (8 days). In human skin equivalents, AP31 favorably influenced cellular pathways known to contribute to skin aging. AP31 positively impacted genes involved in barrier function, skin hydration, skin plumping, and epidermal metabolism. Clinical evaluations of a finished product over 16 weeks demonstrated improvements in jawline sagging, global lift, nasolabial fold appearance, fine lines and wrinkles, smoothness, skin tone, and hyperpigmentation. Subject self-assessment of efficacy was consistent with the clinical grading. No statistically significant changes from baseline in tolerability assessments of edema, erythema, dryness, burning, stinging, itching, or tightness were reported.

Conclusions: AP31 is a novel, multifunctional, non-irritating, cosmeceutical micropeptide that improves clinical signs of aging, lifts and contours facial skin, and reduces inflammation markers.

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INTRODUCTION

There is continuous demand for safe and effective cosmetic ingredients to treat signs of aging skin, such as fine lines and wrinkles, brown spots, discoloration, laxity, and sagging.[1] Multifunctional cosmetic ingredients such as retinol, hydroxy acids, and niacinamide are effective in improving fine lines/wrinkles and in lightening hyperpigmentation but fail to address the changes in facial contour that are a main concern in many individuals.[2-4]

Anti-aging products offering a single mechanism of action may not effectively address some of the most impactful factors contributing to skin aging. These include targeting chronic, low-level inflammation associated with aging, referred to as inflammaging, and boosting normal dermal biosynthesis to maintain a more youthful appearance and overall skin health.[5-8] The facial shape's natural evolution from youth to older appearance involves the following sequential changes: round to oval, then triangular to square, and eventually an inverted triangle as the face becomes increasingly bottom-heavy with age.[9] These changes in contour occur as a result of skin morphologic response to inflammaging, volume loss in the dermis and below,[10] and gravity. Although dermal fillers used for volumetric rejuvenation and surgical lifting procedures are mainstays of treatment for improving facial contour,[9] there is a need for less invasive topical options.

Because they are non-irritating, safe, and versatile, peptides represent a valuable, favored class of cosmeceutical ingredients[11,12] that can be divided into 4 categories: carrier peptides for biologically important molecules, signal peptides that modulate synthesis of extracellular matrix (ECM) components such as collagen and elastin, enzyme-inhibitor peptide, and neurotransmitter-inhibiting peptides with a

neurotoxin-mimetic mechanism of action.[11,12] Given the 21 naturally occurring amino acids, there is great potential for versatility and uniqueness in the molecular composition of cosmetic peptides. However, the ability of peptides to penetrate the skin depends on their molecular weight and net charge at physiologic pH, as well as the fact that they are intrinsically hydrophilic, making the lipid-rich stratum corneum an important barrier that limits bioavailability.[11] Nonetheless, bioavailability can be improved through peptide modifications.

The use of modified peptides for cosmetic benefits dates back to 1973 when Pickart first proposed GHK (glycyl-histidyl-lysine) as a synthetic carrier peptide coupled with copper (Copper Tripeptide-1).[13] Since then, a plethora of peptides designed to target and modulate ECM components have been developed.[14] These peptides are referred to as matrikines and include Pal-KTTKS (palmitoyl pentapeptide-3 or Matrixyl®, 802.07 Da), Pal-tripeptide-3/5 (Syn®-Coll, 578.42/725.94 Da), Pal-GHK + Pal-GQPR (palmitoyl tetrapeptide-7 or Matrixyl® 3000, 888.99 Da), and Pal-tripeptide 38 (Matrixyl® synthe-6, 675.96 Da), in which the palmitoyl moiety, a fatty acid derivative, is attached to enhance stratum corneum penetration.[11,15] Although various clinical studies of signal peptides have confirmed anti-wrinkle benefits at low concentrations,[16-18] low-molecular weight, anti-aging, peptide-based, topical formulations that offer multifaceted anti-aging and anti-inflammatory activity with great tolerability are limited.

Acetyl dipeptide-31 amide (AP31) is a novel multifunctional micropeptide that was developed as part of an 8-year, dermatologist-directed research and development program focused on eczema and skin aging. AP31 (229.3 Da) is similar in size to retinol (286.46 Da), at least 2 times smaller than common marketed anti-aging peptides, and well below the 500-Dalton threshold above which skin penetration and absorption decline rapidly.[19] In addition, its molecular structure was optimized with N-terminus acetylation and amide conversion to further improve stratum corneum penetration.[20] In a study that evaluated penetration of various formulations of AP31 over 48 hours in human cadaver skin samples,[21] AP31 was found to be bioactive and to readily penetrate the skin, whether formulated as a cream, lotion, or water-in-silicone base.

Bioavailability can also be influenced by other variables, and adding a proprietary niosomal carrier, that is, a non-ionic surfactant bilayer vesicle, to the AP31-based formulation enhanced penetration 4 times, compared with the base formulation.[21,22] Studies evaluating the effects of hydroxy acids on the bioavailability of AP31 further showed that a very specific range and type of alpha-hydroxy acid can enhance penetration. For example, 4% glycolic acid was found to enhance skin absorption of AP31 by >4.6 times in a simple emulsion lotion formulation, while 11% glycolic acid unexpectedly decreased it (P<0.05 [4% vs 11%]). The penetration enhancement by glycolic acid did not appear pH related, as no differences in topical bioavailability were observed for the base formulations without glycolic acid at pH 3.8 (adjusted with HCl) and pH 4.9 (unadjusted). It is also notable that penetration enhancement did not occur with other hydroxy acids tested, such as gluconolactone and mandelic acid.[23]

Summarized herein are findings of preclinical and clinical studies that evaluated the anti-inflammatory, anti-aging, lifting, and contouring benefits of AP31, as well as its tolerability, to understand the impact of this novel micropeptide as a multifaceted, cosmetic, anti-aging ingredient.

MATERIALS AND METHODS

Preclinical Study of the Impact of AP31 on Proinflammatory Markers

To investigate potential associations between AP31 and anti-inflammatory mechanisms of action, inhibition of the release of interleukin-4 (IL-4), IL-6, IL-8, IL-17, and tumor necrosis factor alpha (TNFα) by AP31 was compared with that of dexamethasone, a prescription corticosteroid,[24] and tacrolimus, a non-steroidal anti-inflammatory agent.[25]

Human endothelial cells were treated with 1 mM nickel sulfate (Sigma Aldrich, St. Louis, MO), a contact allergen.[26] Human peripheral blood mononuclear cells were treated with anti-CD3 and anti-CD28 antibodies (Invitrogen, Carlsbad, CA) to trigger T-cell receptor (TCR) activation and T cell proliferation, mimicking an allergic reaction.[27] Human epidermal keratinocytes were treated with 5 ng/mL of 12-O-tetradecanoylphorbol-13-acetate (TPA; Sigma Aldrich) to mimic chemical irritation/inflammation.[28] For all experiments (each performed in triplicates), AP31 (at 0.1, 1, 10, and 100 µM), dexamethasone (0.1-100 µM; Sigma Aldrich), tacrolimus/FK506 (0.1-100 µM; Sigma Aldrich), and the vehicle control were solubilized with dimethyl sulfoxide (DMSO) and diluted with cell culture medium. After 24 hours of treatment with AP31, dexamethasone, tacrolimus, or vehicle, conditioned medium was collected from each culture and processed for detection/quantitation of IL-4, IL-6, IL-8, IL-17, and TNFα using enzyme-linked immunosorbent assay (ELISA) protocols and kits from BD Biosciences (IL-4, IL-6, IL-8, and TNFα; San Jose, CA) and Thermo Fisher Scientific (IL-17; Waltham, MA).

Preclinical Studies of the Effects of AP31 on ECM Component Levels

The effects of AP31 0.01% on expression of ECM components were compared with vehicle control in cultures of normal adult human dermal fibroblasts. The 5 ECM components included collagen, known to provide tensile strength and firmness to the skin,[29] decorin, which regulates collagen matrix assembly and is associated with skin strength and resiliency,[30-32] elastin, which allows the skin to stretch and bounce back,[29] fibronectin,

an anchor that connects ECM and membrane proteins,[33] and hyaluronic acid, which binds and retains water, improving skin moisture and plumpness.[34,35] AP31 and the vehicle control were solubilized in DMSO and diluted with cell culture medium for all experiments, each performed in triplicates. After a 72-hour incubation with one dose of AP31 (0.01% final) or vehicle, conditioned medium was collected from each culture and processed for detection/quantitation of procollagen I and hyaluronic acid using the ELISA kits MK101 (Takara Bio USA, San Jose, CA) and K-1200 (Echelon Biosciences, Salt Lake City, UT), respectively. After removal of the conditioned medium, the ECM was extracted (per standard biochemical procedure) and used to quantitate fibronectin, elastin, and decorin with the ELISA kits ab181419 (Abcam, Cambridge, UK), BG-HUM10822 (Novatein Biosciences, Woburn, MA), and ab99998 (Abcam), respectively.

To assess whether AP31 could increase expression of ECM biomarkers ex vivo and thus replicate the effects observed in vitro, 13 human abdominal skin explants 10 mm in diameter were obtained from a 38-year-old Caucasian female donor; 12 were topically treated with 4 µL of AP31 0.01% cream every 48 hours over 8 days, while one was left untreated and served as control. In both groups, the culture medium was replaced every 48 hours. The explants were then processed for standard immunohistochemistry. Detection of collagen III was antibody based (#NBP105119; Novus Biological, Centennial, CO). Elastin detection was based on standard Luna histological stain.[36] Image J software (National Institutes of Health, Bethesda, MD) was used to quantitate the signals' intensity.

Preclinical Study of the Effects of AP31 on Gene Expression

Previous transcriptomics analyses demonstrated that AP31 delivered consistent skin bioactivity across a variety of product formulations, including those with biodelivery enhancers and optimized pH.[21] Herein, whole transcriptome analysis was performed on full-thickness human skin equivalents (3 replicates per group) that were treated once daily for 2 days with 6 µL of AP31-containing formulations at concentrations of 0.1%, 0.5%, and 1% in various bases (eg, cream base with and without pH optimization and cream base with biodelivery modifiers). RNA extraction, assessment for quality, and enrichment, as well as complementary DNA synthesis, amplification by polymerase chain reaction following fragment selection, and Illumina sequencing, were performed by Novogene Co., Ltd. Differentially expressed genes were then analyzed using gene ontology to identify enriched biological processes modulated by AP31, and compare bioactivity among the different AP31 formulations. The Pearson correlation coefficient was used to determine the level of similarity in gene expression across samples and treatments. The findings were also compared with published data showing transcriptomic changes of aging skin and gene expression changes that differentiate younger vs older-looking skin.[37,38]

Clinical Study of the Effects of AP31-Containing Formulation on Signs of Facial Skin Aging

A prospective, single-arm, single-center, 16-week study was conducted with 38 women (per protocol/analysis population; Table 1) who were 40 to 65 years of age and had a Fitzpatrick skin type of I to IV. Additional inclusion criteria included mild-to-moderate jawline sagging (scored 3.0-5.0), mild-to-moderate wrinkles (scored 3.0-5.5), and moderate fine lines (scored 4.0-6.0) per a modified Griffiths scale in which 0 = none and 9 = severe;[39] and having received no treatments from a physician or skin care professional to improve the appearance or firmness of the neck and facial skin within 6 months of study initiation.

At the screening visit, subjects were instructed to avoid application of any topical moisturizing products to the face and neck for ≥3 days before the baseline visit. After completion of the baseline assessments, subjects were instructed to wash their neck and face with their regular nonmedicated cleanser, apply the provided AP31 cream, at least a dime-size amount, on their neck and face, including under the jawline, and allow it to absorb before applying the provided sunscreen lotion (SPF 35). This routine was to be performed every morning and evening for 16 weeks, except the sunscreen application, which occurred in the mornings only. The face cream contained AP31 0.4% with a niosomal carrier and a low concentration of glycolic acid, combined with other beneficial ingredients (acetyl tyrosinamide + gluconolactone).

TABLE 1.

Demographics and Baseline Characteristics of the Analysis Population of the 16-Week Study

	Per Protocol Population (N = 38)[a]
Mean age (SD), y	54.5 (5.7)
Min-max	44-64
Female, n (%)	38 (100)
Ethnicity, n (%)	
Hispanic or Latino	1 (2.6)
Not Hispanic or Latino	37 (97.4)
Race, n (%)	
American Indian or Alaska Native	1 (2.6)
Asian	4 (10.5)
Black or African American	1 (2.6)
White or Caucasian	32 (84.2)
Fitzpatrick skin type, n (%)	
I	1 (2.6)
II	13 (34.2)
III	20 (52.6)
IV	4 (10.5)

SD, standard deviation
[a]Four additional patients were enrolled but were not analyzed due to noncompliance (n = 2) or lost to follow-up (n = 2).

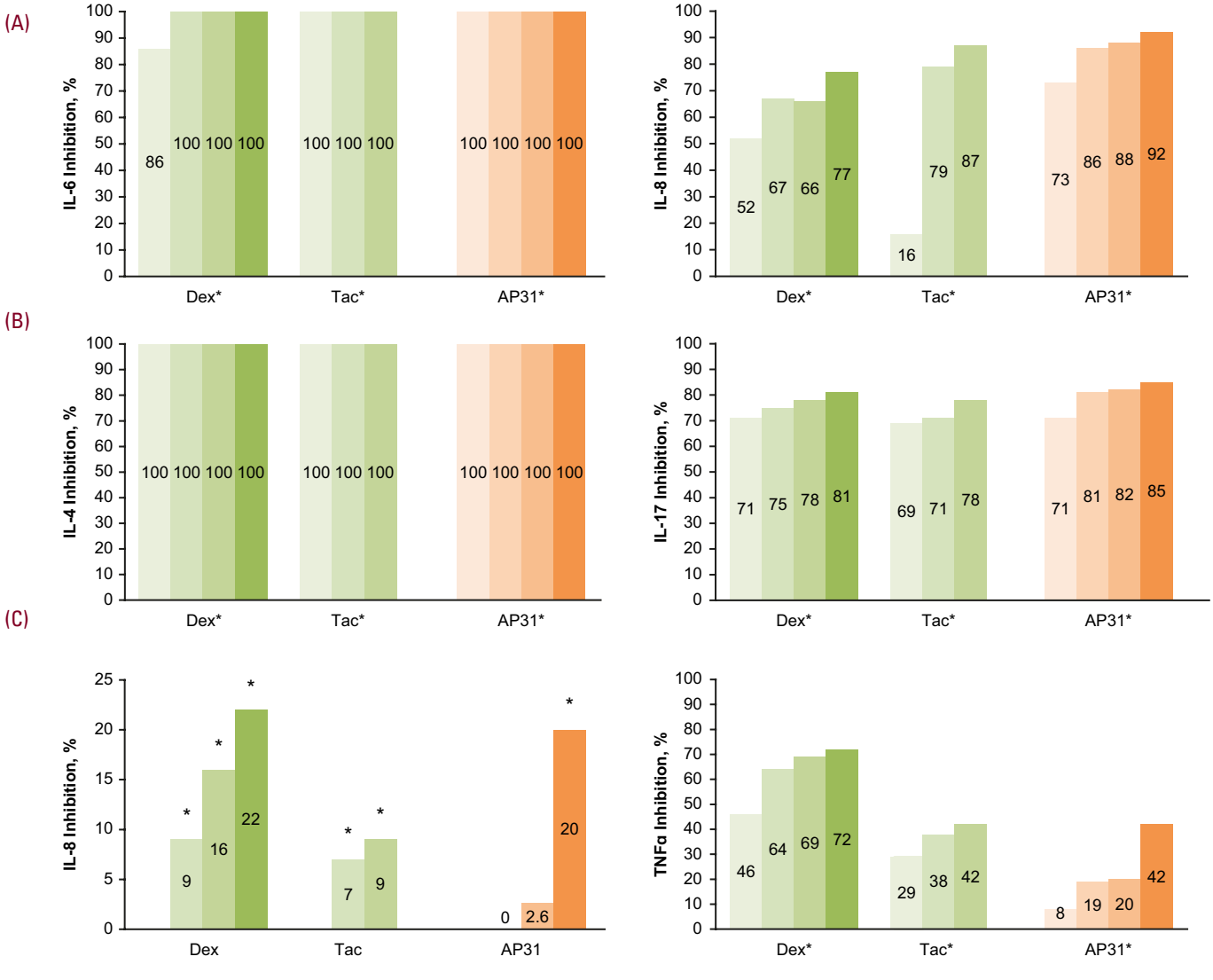
The composite primary endpoint was clinical grading of efficacy at week 16 per the following parameters: fine lines, wrinkles, pore size, visual roughness, tactile roughness, laxity, jawline sagging, global lift, appearance of nasolabial folds, hyperpigmentation, skin tone evenness, skin clarity, skin radiance/brightness, and overall skin appearance (global face and crow's feet). Secondary endpoints included clinical grading of the same efficacy parameters at weeks 2, 6, and 12. Subject self-assessment of AP31 included 13 items rated based on the level of visible improvement of their skin on a 1 to 5 scale (1 = excellent; 5 = poor or none). The items included skin tightening, revival, radiance, fullness, firmness, elasticity, and hydration, as well as facial and jawline contouring, appearance of fine lines/wrinkles, and whether their skin felt younger looking. Tolerability was also evaluated at each visit.

RESULTS

Preclinical Findings: Effects of AP31 on Proinflammatory Markers

In human endothelial cells exposed to nickel for 24 hours, AP31, dexamethasone, and tacrolimus statistically significantly reduced release of IL-6 (86%-100%) and IL-8 (≥52% for all doses except tacrolimus 0.1 μM [16%]), compared with the vehicle control (P<0.05 for all; Figure 1). Similarly, statistically significant inhibition of IL-4 and IL-17 release was observed in

FIGURE 1. Inhibition of inflammatory mediators in (A) nickel-treated human endothelial cells, (B) T-cell receptor–activated human peripheral blood mononuclear cells, and (C) 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced human epidermal keratinocytes after treatment with 4 concentrations of AP31 (0.1, 1, 10, and 100 μM), dexamethasone (Dex; 0.1, 1, 10, and 100 μM), or tacrolimus (Tac; 0.1, 1, 10, and 100 μM) for 24 hours, compared with the vehicle control.



In the graphs, the lightest colors represent the lowest concentrations of agents tested, while the darkest colors represent the highest concentrations. The inhibitory effect of tacrolimus 100 μM could not be evaluated due to cytotoxicity. *P<0.05 vs vehicle. AP31, acetyl dipeptide-31 amide; IL, interleukin; TNF, tumor necrosis factor.

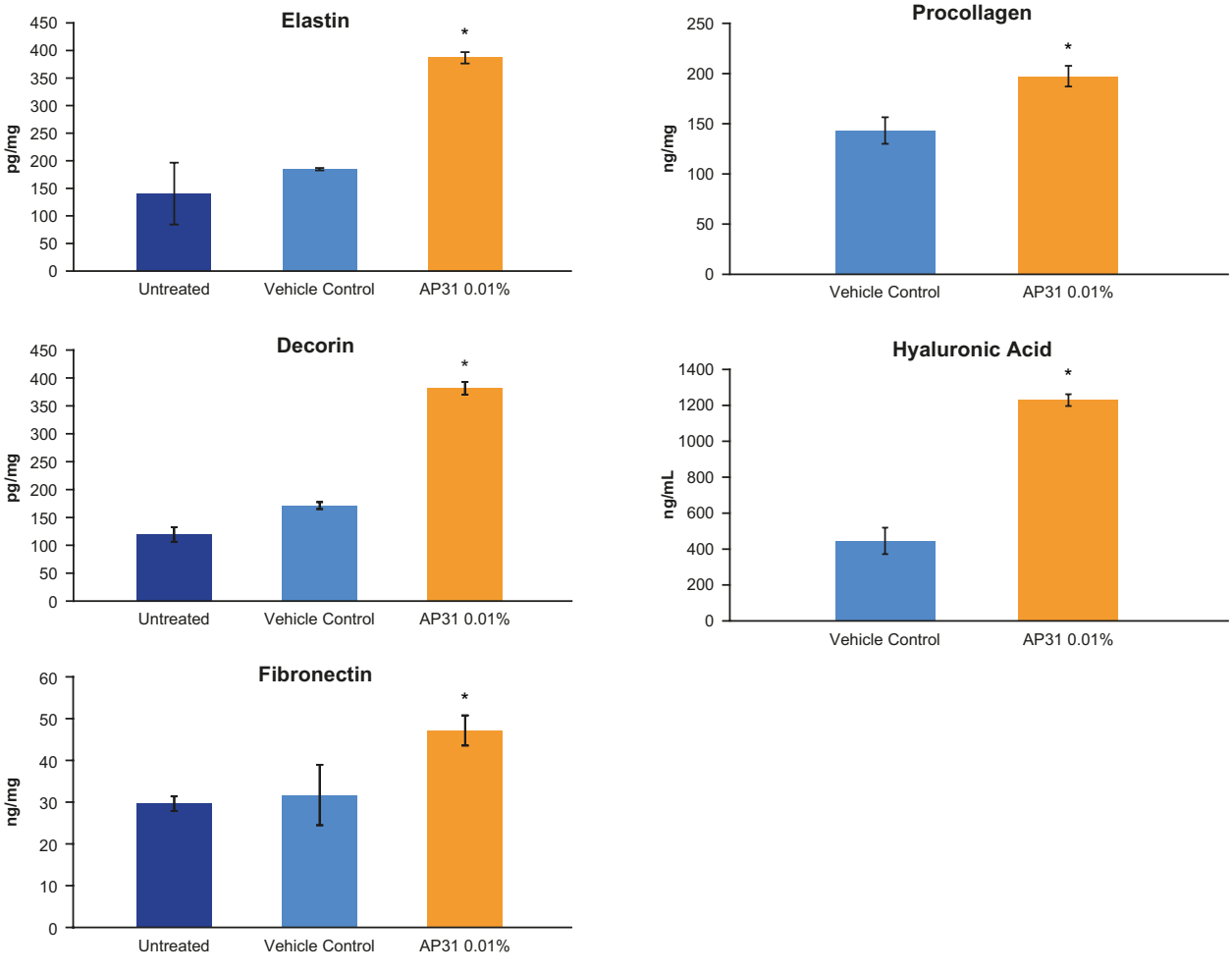
TCR-activated peripheral blood mononuclear cells treated with AP31, dexamethasone, and tacrolimus, compared with vehicle (P<0.05 for all; Figure 1). In epidermal keratinocytes exposed to TPA, statistically significant inhibition of IL-8 and TNFα release was also observed in the presence of AP31 (100 μM only for IL-8), dexamethasone, and tacrolimus, compared with vehicle (P<0.05 for all; Figure 1). Notably, AP31 100 μM appeared nearly as effective as dexamethasone and tacrolimus in all 3 models (Figure 1), but showed no signs of cytotoxicity, compared with tacrolimus 100 μM.[40,41]

Preclinical Findings: Effects of AP31 on ECM Component Levels

In normal adult dermal fibroblasts exposed to AP31 0.01% for 72 hours, statistically significant increases in elastin, decorin, fibronectin, procollagen, and hyaluronic acid levels were observed, compared with vehicle controls (P<0.05 for all; Figure 2), without deleterious effects on cell viability or metabolism.[40,41]

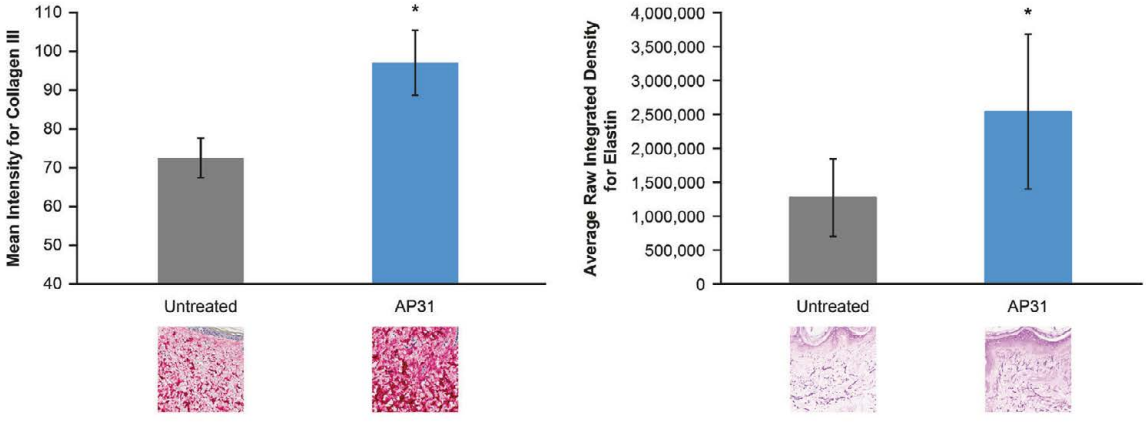
In human skin explants treated with AP31 0.01% in formulation for 8 days, collagen and elastin protein levels were also statistically significantly increased, compared with untreated samples (P<0.05; Figure 3).

FIGURE 2. Levels of extracellular matrix biomarkers in normal adult human dermal fibroblasts treated with AP31 0.01% or vehicle for 72 hours.



*P<0.05 vs vehicle.
AP31, acetyl dipeptide-31 amide.

FIGURE 3. Collagen III and elastin levels in human skin explants treated or not with AP31 0.01% in formulation every 2 days for 8 days (as described in the Methods section).

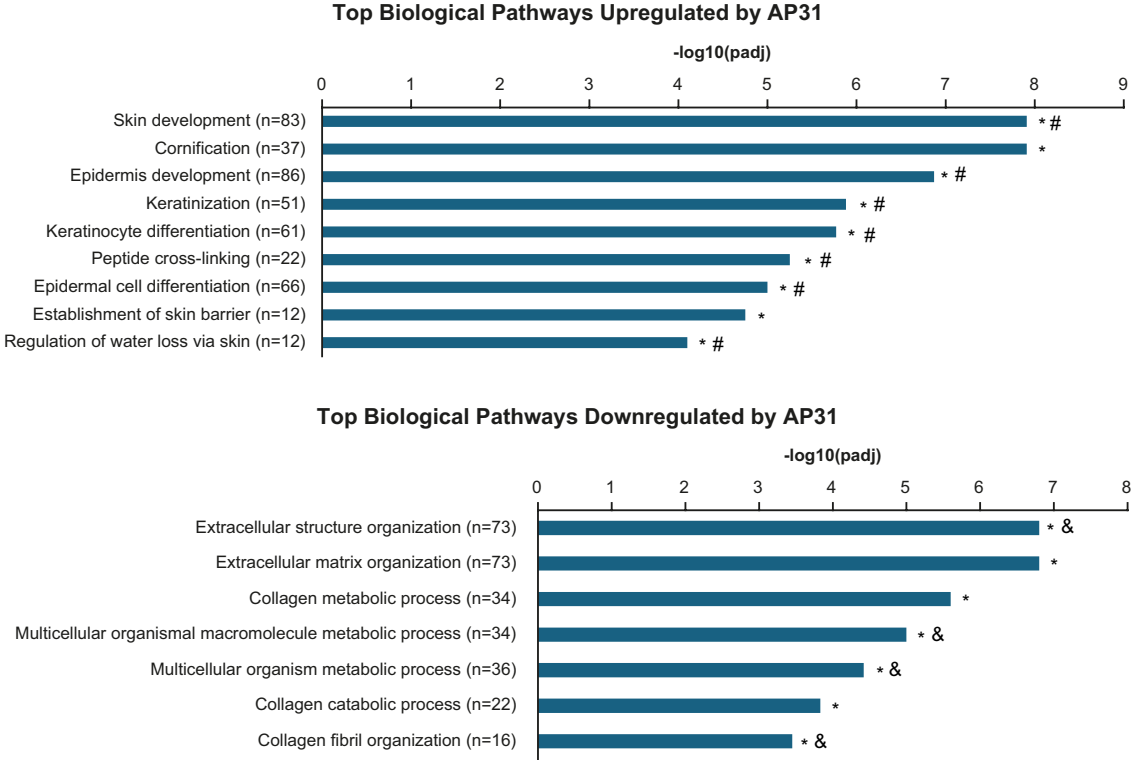


*P<0.05 vs untreated controls.
AP31, acetyl dipeptide-31 amide.

Preclinical Findings: Effects of AP31 on Gene Expression

In full-thickness human skin equivalents treated with AP31 or left untreated, AP31 0.1% and 0.5% in the cream base demonstrated the highest enhancement of skin-related gene ontology terms, including skin development, epidermis development, epidermal cell differentiation, keratinization, keratinocyte differentiation, and peptide cross-linking that were upregulated with both concentrations of AP31. The AP31 0.1% cream upregulated 7 top pathways that were previously shown to be downregulated in normal skin aging and downregulated 4 pathways that were previously shown to be upregulated in skin aging (Figure 4).[37] In addition, individual gene analysis revealed a positive impact

FIGURE 4. Top biological pathways for which gene expression was upregulated or downregulated after treatment of full-thickness human skin equivalents with AP31 0.1% (once daily for 2 days).



*P<0.05. n indicates the number of genes significantly enriched in the biological pathway as a result of AP31 0.1% treatment. # highlights the pathways previously reported as downregulated with aging.[37] & highlights the pathways previously reported as upregulated with aging.[37]
AP31, acetyl dipeptide-31 amide; padj, adjusted P value (the smaller the value, the more significant are the differentially expressed genes).

of AP31 on expression of many genes (Table 2), including those involved in barrier function (eg, peptidyl arginine deiminase 1 [*PADI1*]), skin hydration (eg, aquaporin-5 [*AQP5*]), skin plumping (eg, hyaluronan synthase 3 [*HAS3*]), and epidermal metabolism and senescence downregulation/inhibition (eg, glutamate dehydrogenase 1 [*GLUD1*] and cyclin-dependent kinase inhibitor 2A [*CDKN2A*], respectively).

Clinical Study Confirms Anti-Aging, Firming, Contouring, and Lifting Benefits of AP31

All 15 clinically graded parameters were significantly improved at weeks 12 and 16 ($P<0.01$), and 7 were improved as early as week 2 ($P<0.01$).[23] Most notable were the improvements in lower face attributes, including jawline sagging, global lift, and the appearance of nasolabial folds at 16 weeks (Figures 5-6). Fine lines and wrinkles, smoothness, and skin tone were also improved (Figure 7).

Subject self-assessment of efficacy was consistent with that based on expert clinical grading. As early as week 2, 94% of subjects noted firmer, more elastic skin. Of the 13 facial attributes self-assessed at week 2, 11 were deemed to have improved by ≥86% of subjects, and 2 (jawline and facial definition/contouring) were deemed to have improved by 76% of subjects. At week 16, 92% noted improvement in their jawline and facial contouring. Of the 16 facial attributes self-assessed at week 16, 14 were deemed to have improved by ≥94% of subjects, demonstrating noticeable benefits of the AP31-containing product across the study population.

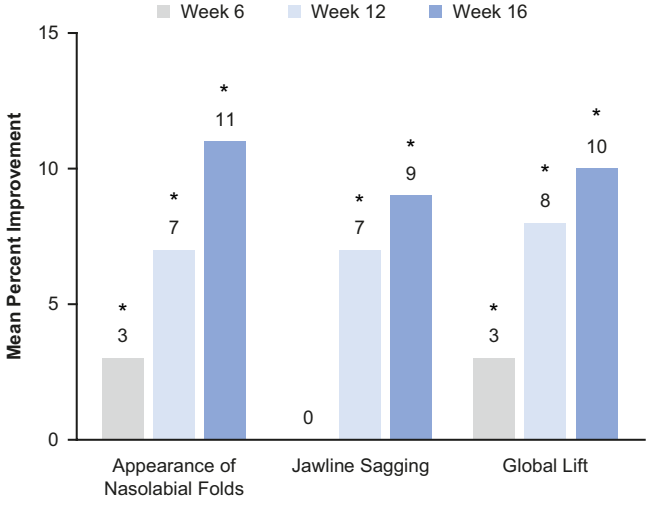
TABLE 2.

Effects of AP31 0.1% on Individual Gene Expression

Gene	Biological Function	Potential Skin-Related Benefits	Fold Change (Relative to Untreated Samples)
GLUD1	Epidermal energy metabolism	Visible signs of skin aging (eg, wrinkling)	2.09
CDKN2A	Cell senescence (physiological age marker)		0.74[a]
AQP5	Hydration, water channel protein	Hydration, plumping	6.77
HAS3	Hydration		2.25
PADI1	Epidermal barrier, differentiation, hydration	Epidermal barrier, skin mechanical resistance and structural stability	8.11
ITGB7	Dermal-epidermal junction		4.34
TGM1	Epidermal barrier		2.24
IVL	Epidermal barrier		1.80
LIPN	Lipid metabolic process		1.93

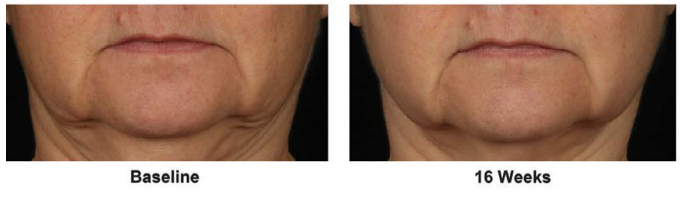
[a]The lower number reflects the anti-aging properties of AP31, as reflected by the decreased expression of the cell senescence marker *CDKN2A*. *AQP5*, aquaporin-5; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *GLUD1*, glutamate dehydrogenase 1; *HAS3*, hyaluronan synthase 3; *ITGB7*, integrin subunit beta 7; *IVL*, involucrin; *LIPN*, lipase family member N; *PADI1*, peptidyl arginine deiminase 1; *TGM1*, transglutaminase 1.

FIGURE 5. Clinical improvement from baseline in aging parameters of the lower face following use of AP31 0.4% cream twice daily for 16 weeks.



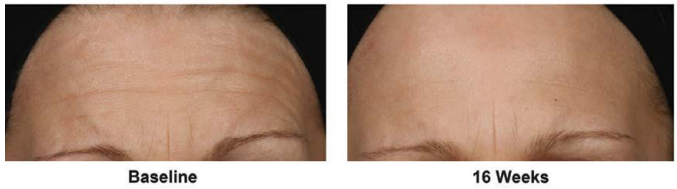
*$P<0.01$.
AP31, acetyl dipeptide-31 amide.

FIGURE 6. Improved jawline contour and lift of the lower face following use of AP31 0.4% cream twice daily for 16 weeks, compared with baseline.



AP31, acetyl dipeptide-31 amide.

FIGURE 7. Diminished lines and lift on the forehead following use of AP31 0.4% cream twice daily for 16 weeks, compared with baseline.



AP31, acetyl dipeptide-31 amide

AP31 Toxicity/Tolerability

In preclinical studies, no AP31-related cytotoxicity was observed. In clinical studies, the product was well tolerated, with no reports of product-related adverse events and no statistically significant changes from baseline in tolerability assessments of edema, erythema, dryness, burning, stinging, itching, and tightness.

DISCUSSION

Considering the reported association between inflammaging and ECM alterations,[42,43] as well as the anti-inflammatory effects of AP31 observed herein in in vitro models, we hypothesized that AP31 could provide anti-aging benefits by increasing the levels of ECM-associated anti-aging components while being gentle and suitable for daily use.

In vitro,[40] AP31 modulated 5 ECM components known to confer the bulk of biomechanical and viscoelastic properties in young, healthy skin.[35,44,45] Compared with the vehicle control, AP31 indeed increased the levels of elastin,[29] decorin,[30,31] fibronectin,[33] collagen,[29] and hyaluronic acid[34,35] at 72 hours. Notably, the positive effects of AP31 on ECM components were also observed in skin explants after 8 days of treatment. Moreover, AP31 demonstrated pleiotropic effects on gene expression, with key pathways being upregulated and downregulated similarly as previously reported in younger skin.[37,38] In fact, AP31 demonstrated significant stimulatory effects on genes associated with cellular metabolism, as well as inhibitory effects on the expression of genetic markers of cell senescence. Genes associated with cellular metabolism have been shown to be downregulated more significantly with age.[38] The inhibitory effect of AP31 on the genetic marker of cell senescence *CDKN2A* is particularly important because cell senescence has been shown to increase significantly in photo-exposed skin, and it is thought that even small proportions of senescent cells can contribute to visible signs of aging and their underlying biological processes, including inflammation and oxidative stress.[38,46,47]

Clinical evaluation of the effects of AP31 applied to the face and neck over 16 weeks indicated improvements in jawline sagging, global lift, and the appearance of nasolabial folds, fine lines, and wrinkles, as well as skin smoothness, tone, and hyperpigmentation. Per the self-assessment of AP31's efficacy, at least three-quarters of subjects reported improvements in all skin attributes, including the jawline, at week 2, and 94% reported firmer, more elastic skin. At week 16, ≥94% reported improvement in most skin attributes, including their jawline and contour of their lower face. Moreover, there were no product-related adverse events or statistically significant changes from baseline in tolerability assessments.

Previous studies demonstrated that AP31 was readily absorbed and that delivery can be optimized through formulation design.[41] The current study findings indicate that previously identified matrix-building, anti-inflammatory, and other anti-aging biological processes were favorably modulated by AP31. Thus, it appears that AP31 has the potential to rejuvenate the skin by modulating these pathways so as to mimic a younger skin. In view of its demonstrable anti-inflammatory activity and excellent tolerability, AP31 should be an appealing anti-aging ingredient for individuals with clinically sensitive skin. It is of interest that a previous double-blind, active-controlled clinical study was conducted to evaluate the effects of AP31 1.0% vs desonide 0.05% creams in reducing skin symptoms of mild-to-moderate eczema/atopic dermatitis.[48] After 3 weeks of treatment, AP31 statistically significantly improved the symptoms of eczema, and there were no differences in tolerability and efficacy between treatments.[48]

The data reported herein are also of interest because of the growing demand for gentle, effective cosmetic ingredients that will not only improve the appearance of aging skin[49] but preserve youthful skin qualities in the emerging pre-aging population as well. Although pre-aging remains a relatively new concept, textural and pigmentation changes such as fine lines, dullness, uneven skin tone, and visible skin pores are often identified as early pre-aging signs that occur before the typical aging signs such as wrinkles, brown spots, and sagging become apparent.[1,50-52] The pre-aging phase can start in the mid-20s to early 30s (or even earlier[51]), and it is characterized by changes that consumers often do not yet classify as obvious signs of aging.[1,50,51,53] To help delay signs of aging and maintain youthful skin appearance and function, it is important to preserve dermal matrix components, which can be achieved by healthy lifestyle factors including sun protection, good sleep, lowering psychological stress, no smoking, and proper nutrition.[51] A gentle volume-building ingredient like AP31 that helps mitigate downstream consequences of inflammaging and oxidative stress through inhibition of senescence markers and stimulation of ECM components may be beneficial in protecting and preserving the skin attributes associated with youth in the pre-aging population.

A potential limitation of this work is that different concentrations of AP31 were used across studies, due to the type of studies and their timing. However, AP31 did not result in cytotoxicity or tolerability issues in any of the studies reported, regardless of concentration. Additional research on pre-aging individuals will help further understand the impact of AP31 on this population.

CONCLUSION

The data presented herein demonstrate that AP31 is a novel, unique, signaling micropeptide with broad anti-aging benefits. The inhibition of proinflammatory cytokines, enhancement of ECM component levels, and reactivation of a younger skin-like gene expression profile induced by AP31 are consistent with

anti-aging properties, as evidenced by clinician-graded and self-assessed improvements in several skin attributes typically associated with aging. AP31 also appears to expand the breadth of anti-aging options beyond that of other widely used agents, such as retinol and alpha hydroxy acid, reducing fine lines and wrinkles while improving the facial and jawline contour, among other benefits. Being non-irritating and well tolerated, AP31 can be used by individuals seeking gentle anti-aging alternatives. Moreover, due to its unique ability to modulate proinflammatory pathways and inflammaging, senescence, metabolism, and ECM components, AP31 may not only improve the appearance of aging skin but preserve youthful skin qualities in the pre-aging population as well.

DISCLOSURES

BLE, RP, MD, NKT, and BAG are employees of Kenvue Brands LLC. PKF has served as an advisory board member and consultant to Kenvue Brands LLC.

Funding: The study was supported by Kenvue Brands LLC.

Ethics Statement: The protocol of the clinical study was reviewed and approved by IntegReview Institutional Review Board (Austin, TX) before study initiation. Each study subject provided written informed consent before undergoing any study-related procedures/assessments.

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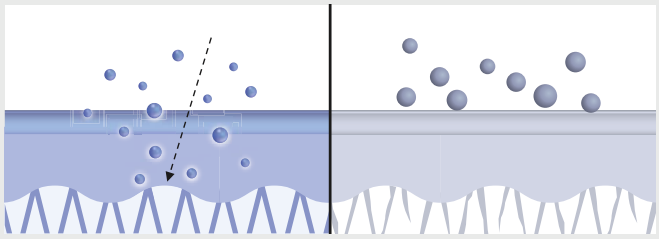

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Gene Analysis of Biostimulators: Poly-L-Lactic Acid Triggers Regeneration While Calcium Hydroxylapatite Induces Inflammation Upon Facial Injection

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ABSTRACT

Background: Injectable biostimulator treatments stimulate endogenous collagen in aging skin, but whether they act through similar pathways is unknown. This study evaluates 2 biostimulatory agents' effects on genes, expressed proteins, and respective pathways as potential aging biomarkers and treatment outcomes.

Methods: This 13-week, randomized, single-center, comparative study compared volume change and gene expression stimulated by poly-L-lactic acid (PLLA-SCA™) and calcium hydroxylapatite (CaHA-R) via punch biopsy in the nasolabial fold (NLF). Subjects (n=21) had shallow NLF contour deficiencies on the wrinkle assessment scale (WAS) ≥2 and identical WAS scores on both sides of the nose. Biopsies at baseline and 90 days were analyzed for gene expression of targeted biomarkers. These results were assessed using the STRING and Reactome databases to determine functional pathways, as well as gene markers and their respective pathways.

Results: Gene analysis suggested unique processes for each biostimulator. PLLA-SCA stimulated more components of the extracellular matrix with less inflammatory response, translating to a more regenerative pathway. CaHA-R elicited a more inflammatory response that could diminish tissue regeneration, translating to a pro-inflammatory pathway.

Conclusions: PLLA-SCA is associated with regenerative pathways, while CaHA-R did not show evidence of tissue regeneration and upregulated more genes in pro-inflammatory pathways.

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INTRODUCTION

Aging skin is characterized by dermal thinning with collagen, elastin loss, and altered fat volume and distribution.[1,2] These changes occur due to the degradation of the skin's structural components with function alteration due to intrinsic and extrinsic factors.[3,4]

The epidermis and dermis atrophy are due to decreased and inefficient mast cells and fibroblasts, which are key to structural alterations, including diminished collagen, proteoglycans, and elastin.[3,4] Senescent fibroblasts create a pro-aging microenvironment.[5] In pro-aging environments, matrix metalloproteinases (MMPs) are activated, accelerating extracellular matrix (ECM) breakdown and suppressing growth factor release.[3] In addition, complex negative feedback loops occur due to abnormal collagen and elastin metabolism, increasing MMPs and furthering ECM degradation.[3,6] Superficial and deep facial fat compartments are also altered.[7] Fat can reposition, which is most apparent in the jowl, lateral nasolabial fold (NLF), and labiomental crease.[7]

When selecting treatments, it is important to consider regeneration. Regenerative pathways activate multiple systems that help restore the tissue's natural architecture and function. Treatments that offer tissue replacement primarily result in connective tissue deposition, which does not translate to natural morphology or function.[3] Regenerative aesthetics focuses on the recreation of normal/youthful functioning tissue.[3] An important step toward regenerative aesthetics approaches includes identifying potentially regenerative treatments.[3] Regenerative approaches use cells, bio-cues, and scaffolds.[3] Scaffolds may be regenerative or non-regenerative. Regenerative scaffolding can stimulate structural tissue components, while non-regenerative scaffolds lead to narrow tissue-type formation.[3]

Poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) are both commonly used aesthetic treatments.[4] Soft-tissue injectables are popular because they are minimally invasive and are effective for restoring volume and correcting contour deficiencies.[8] PLLA-SCA™ (Sculptra®, Galderma Laboratories,

L.P, Galderma, Sweden) is a biostimulator, and CaHA-R (Radiesse® (+) (Merz Aesthetics, Raleigh, NC) is a biostimulatory agent; however, PLLA-SCA® lasts for up to 25 months post-treatment[18] while CaHA-R lasts a year or more.[22,23] Both treatments are currently FDA-approved in the United States for the correction of facial wrinkles and NLFs, but it is unknown whether they have similar cellular and molecular pathways, particularly regarding neocollagenesis and ECM remodeling.[9,10] This study was designed to evaluate cellular and molecular pathways occurring at the genomic level that contribute to ECM changes. Clinical photography (3D and 2D) was also used to monitor volume changes in the NLFs.

MATERIALS AND METHODS

This was a randomized, single-center, comparative study of PLLA-SCA administered in two treatments (baseline [BL] and week 4) vs CaHA-R for one treatment with an optional second treatment (BL and week 4) to achieve optimal correction. To collect tissue for gene expression analysis, a 3-mm punch biopsy was taken at BL and day 90. The study was conducted in accordance with good clinical practice and obtained Institutional Review Board (IRB) approval on September 8th, 2022 (IRB ID: 10350, clinicaltrials.gov number: NCT05620043). All subjects provided written informed consent.

Patient Population

To be eligible for inclusion, subjects were of any race/ethnicity/Fitzpatrick skin phototype, men or women aged 22 to 50 years, with healthy immune systems. Subjects must have minimum shallow NLF contour deficiencies assessed by wrinkle assessment scale (WAS) ≥2 (range 0-5 with 0=no visible, minimal wrinkles and 5=very deep wrinkles, redundant folds), with identical WAS scores on both sides and an anticipation of 2 treatments for optimal clinical outcomes. Individuals were excluded from participating if they had significant NLF asymmetry or different WAS scores on either side of the nose. In addition, subjects who were or were planning pregnancy were excluded along with those who had any of the following: history of allergy/hypersensitivity, bleeding disorder, excessive bleeding after medical procedures, use of blood thinning medications, prescription facial wrinkle therapy or topical steroid applied to the NLF, use of immunosuppressive medications or systemic steroids, history of skin infections, current use of supplements or homeopathic medications, history of keloids, implant in treatment area, filler use or other facial treatment/procedure with 12 months prior to baseline, history of facial nerve palsy, or current smokers.

Assessments

Clinical grading of NLF was performed at BL for screening purposes using a WAS. A 3-mm punch biopsy was performed at BL and day 90 using the standard technique. The biopsy was taken from the NLF crease after randomization for which side served as the baseline and day 90 biopsy. Study assessments focused on gene expression for the following biomarkers: scar tissue formation, collagen, elastin, ECM integrity, epidermal barrier function, anti-aging, antioxidant, cell renewal/regeneration, inflammation, growth factor, and hydration. Biopsy samples were preserved in ribonucleic acid (RNA) later and sent for RNA isolation and gene expression analysis on an icepack or dry ice. Samples were analyzed by Genemarkers, LLC (Kalamazoo, MI) using a selected panel of skin biomarkers. The gene analysis procedure isolated RNA from each biopsy, then cDNA was synthesized from the RNA and preamplified for quantitative polymer chain reaction (qPCR) processing. qPCR reactions were run, and each gene was assayed in duplicate. For data analysis, qPCR data quality and statistical analysis were assessed and performed on raw data files. Finally, STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) analysis was conducted on differentiated genes.[18] The genes identified by the Genemarkers analysis to be upregulated were subjected to the STRING and Reactome databases for analysis.[18,19]

STRING is a biological database and web resource for known and predicted expressed protein-protein interactions.[18] The STRING database includes experimental data, computational prediction methods, and public text collections.[18] It also can be used to identify functional enrichments in user-provided lists of proteins/genes, using functional classification systems such as Gene Ontology (GO), Pfam, and Kyoto Encyclopedia of Genes and Genomes (KEGG).[18] The Reactome is a database of biological pathways that includes bioinformatics tools for analyzing, interpreting, and visualizing the mechanisms involved in biological pathways.[19] These tools were used to assess pathways and functions related to the genes that were significantly upregulated.

Using the Cherry Imaging device (Cherry Imaging, Israel), 3D photography at BL, day 28 prior to treatment and day 90 prior to biopsy was performed to assess volume changes. Adverse events were notated.

Statistical Analyses

Gene expression was compared between treatment products and between BL and day 90. Statistical analysis for gene expression from the Gene markers portion of the study was done by conducting an unpaired t-test using ThermoFisher Connect software (ThermoFisher Scientific, Waltham, MA). The statistical comparison generated the delta delta Cq (dd Cq) values. The software converted the dd Cq values into log and linear relative quantitation (RQ) values. The log RQ values were converted to linear fold-change values. RQ values ≥1 or <1 were used to determine the significance.

RESULTS

Population

A total of 21 subjects participated, with 20 subjects completing the study. Among them, 11 subjects were treated with PLLA-SCA and 10 with CaHA-R. Subject demographics are presented in Table 1 and were generally similar between treatment groups.

Treatment Amounts

All subjects received 2 treatments as indicated per each product's instruction for use with on-label 8 mL dilution for PLLA-SCA with 1 mL lidocaine and a pre-filled syringe with CaHA-R. Each treatment session consisted of multiple deep dermal or subdermal injections at both NLFs. The average injected amount per NLF at baseline (BL) was 2 mL for PLLA-SCA and 1.65 mL for CaHA-R. At day 28 (+/- 3 days), all PLLA-SCA subjects received a second treatment with a mean injected amount of 2.27 mL per NLF. At the Investigator's assessment, all CaHA-R subjects also received a second treatment at day 28 with a mean injected amount of 1.23 mL per NLF. In total (BL + day 28), the mean injection amount was 4.27 mL for PLLA-SCA and 2.88 mL for CaHA-R per NLF, respectively. The treatment amount was at the discretion of the investigator for optimal outcomes and thus did not influence treatment efficacy at the gene level.

Targeted Skin Biomarker Results and STRING Analysis

Both PLLA-SCA and CaHA-R upregulated genes are involved in ECM integrity, inflammatory/immune response, and wound healing (Figure 1 and Table 2). No genes were significantly decreased in expression for either treatment group. Table 2 and Figure 2 shows the genes that were upregulated (from 117 targeted skin biomarkers) at day 90 compared to BL. In this small cohort, a gene was reported to be significantly upregulated if it was found in ≥37% of the subject panel. These sets of genes were explored for functional enrichment and pathway assessment using the STRING and Reactome databases, respectively.

FIGURE 1. PLLA-SCA and CaHA-R specific genes in more than one-third of subjects at 90 days.

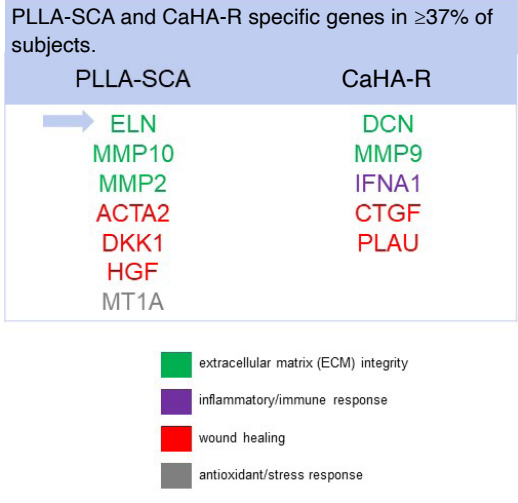


TABLE 1.

Demographic and Baseline Characteristics		
	PLLA-SCA, N (%)	CaHA-R, N (%)
Age		
Mean (y)	46.5	46.4
Range	36-50	43-50
Gender		
Female	10 (90.9%)	7 (70%)
Male	1 (9.1%)	3 (30%)
Race/Ethnic Background		
White/Caucasian	7 (33.3%)	7 (70.0%)
Hispanic/Latin American	14 (66.7%)	3 (30.0%)
Fitzpatrick Skin Type		
I	1 (9.1%)	0
II	5 (45.5%)	6 (60.0%)
III	5 (45.5%)	3 (30.0%)
IV	0	1 (10.0%)
WAS Score		
3 (moderate wrinkles)	5 (45.5%)	4 (40.0%)
4 (deep wrinkles)	6 (54.5%)	6 (60.0%)

TABLE 2.

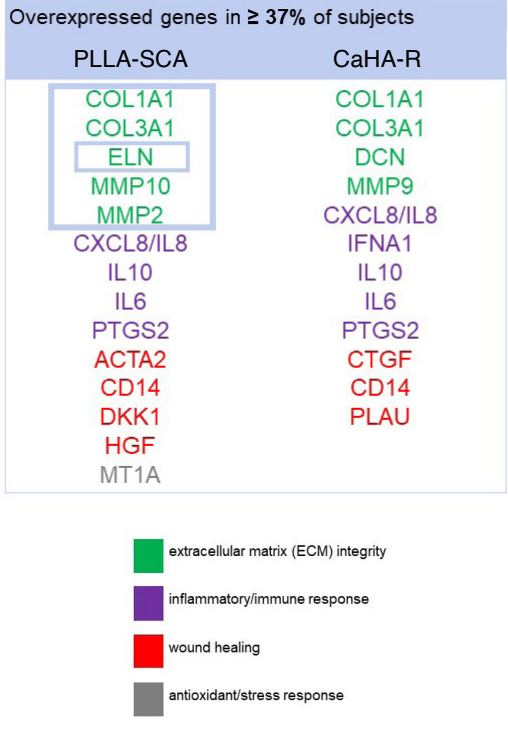
Upregulated Genes at Day 90 Compared to BL From Among 117 Targeted Skin Biomarkers				
Gene function(s)	In ≥50% of the subject panel		In ≥37% of the subject panel	
	PLLA-SCA (n=11)	CaHA-R (n=9)	PLLA-SCA (n=11)	CaHA-R (n=9)
ECM integrity	COL1A1	COL1A1	COL1A1 COL3A1 ELN MMP10 MMP2	COL1A1 COL3A1 DCN MMP9
Inflammatory/immune response	IL10	CXCL8/IL8 IL10 IL6 PTGS2	CXCL8/IL8 IL10 IL6 PTGS2	CXCL8/IL8 IFNA1 IL10 IL6 PTGS2
Wound healing	ACTA2 CD14	CD14 PLAU	ACTA2 CD14 DKK1 HGF	CTGF CD14 PLAU
Antioxidant/stress response	--	--	MT1A	--

TABLE 3.

Gene Ontology Enrichment – Types of Biological Pathways Stimulated by PLLA-SCA and CaHA-R		
Related pathways	PLLA-SCA (%)	CaHA-R (%)
Inflammation	14	18
Pro-inflammatory	5	11
Tissue remodeling/ morphogenesis	16	10
Collagen formation	4	3

*$P<0.05$ per individual % related activity for each treatment product. Statistical analysis was not performed for PLLA-SCA vs CaHA-R.

FIGURE 2. Upregulated genes that were identified at day 90 after treatment.

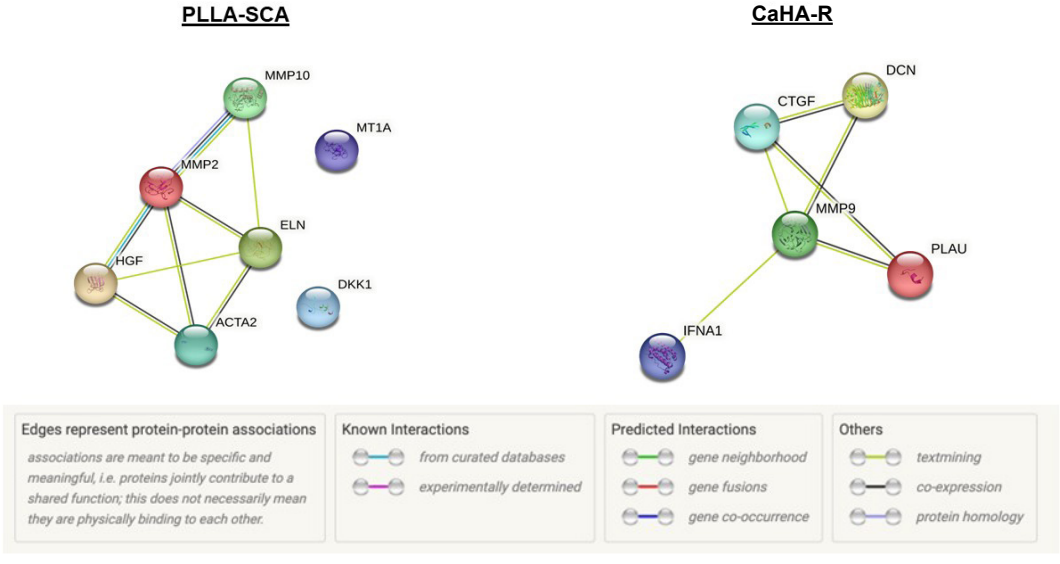


The functional enrichments found by the GO analysis and the pathways identified in the Reactome database (Table 3) revealed that the genes upregulated in the CaHA-R group were associated with inflammation and pro-inflammatory pathways. In contrast, PLLA-SCA exhibited a gene expression profile that was indicative of tissue remodeling and morphogenesis pathways. Both treatments induced expression pathways related to collagen formation. The STRING analysis revealed the central gene involved in the interaction network was elastin (ELN) for PLLA-SCA, which is a regenerative protein. While the central gene for CaHA-R was MMP9, a pro-inflammatory cytokine (Figure 3).

STRING Interactions

Data from STRING interactions indicate that PLLA-SCA stimulated the expression of unique genes relating to morphogenesis. The pluripotent cell differentiation pathways, hepatocyte growth factor (HGF) and Dickkopf -related protein 1 (DKK1) were affected, with HGF representing pluripotent cell differentiation pathways, while DKK1 is associated with pigmentation regulation. PLLA-SCA STRING interactions also suggested upregulation of stem cell differentiation (matrix metalloproteinase 10 [MMP10], actin alpha 2 [ACTA2]), upregulation of ECM remodeling (collagen) and elastin synthesis (ELN, matrix metalloproteinase 2 [MMP2]), as well as upregulation in MET proto-oncogene receptor tyrosine kinase signaling (MMP2, ACTA2, HGF, DKK1, and metastasis-associated 1 [MT1A]) (Figure 3). These are

FIGURE 3. PLLA-SCA stimulates structural morphogenesis. CaHA-R stimulates a response to wound healing. (A) PLLA-SCA pluripotent stem cell differentiation pathway (HGF, DKK1), stem cell differentiation ([MMP10, ACTA2], ECM remodeling/collagen and elastin synthesis [ELN, MMP2], MET signaling [MMP2, ACTA2, HGF, DKK1, MT1A]) at 90 days. (B) CaHA -R stimulates endochondral ossification (MMP9, PLAU), ECM remodeling/collagen (DCN, MMP9), and inflammation (IFNA1, PLAU, CCN2/CTGF, MMP9) at 90 days.



associated with enhanced wound healing, integrity of the ECM, and an antioxidative/stress response.

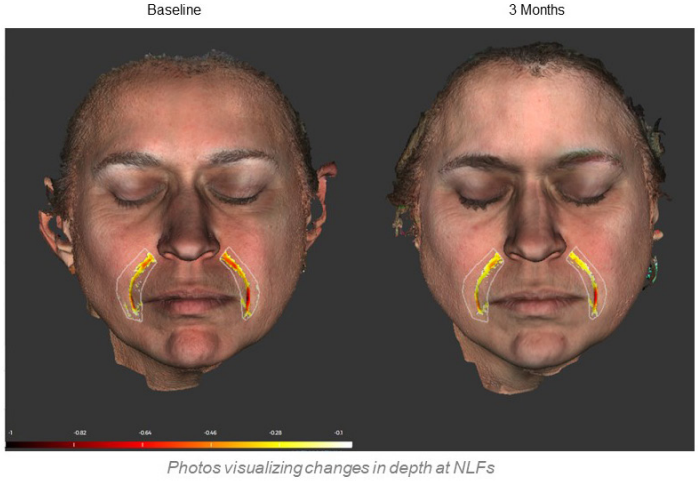
Photographic Results

Both treatments are efficacious, as shown via Cherry Imaging (Figure 4). Photographic results validated the injection procedure and clinical outcomes. The results align with previously described effects to support the gene changes.[8,10]

Safety

No treatment-related adverse events were reported or observed throughout the study. There were biopsy-related adverse events, which included 11 anticipated reactions in 7 subjects, including tenderness, bleeding, erythema, minor pain, and soreness. These were judged by investigators to be related to the biopsy procedure.

FIGURE 4. 3D imaging showing wrinkle depth and volume improvement with PLLA-SCA.



Photos visualizing changes in depth at NLFs

The scale shows depth (darker=deeper, lighter=shallow).

Table 6. Depth and Missing volume		Left NLF	Right NLF
Depth (mm)	Baseline	0.32	0.24
	3 Months	0.25	0.23
	Change in Depth	-0.07	-0.01
Missing Volume (mm^3)	Baseline	44.5	32.5
	3 Months	33.8	28.5
	Change in Missing Volume	-10.7	-4

- Depth was calculated as average.
  - Decrease in depth = improvement.
- Missing volume was calculated as total.
  - Decrease in missing volume = improvement.

DISCUSSION

The PLLA-SCA and CaHA-R treatments led to gene upregulations involved in collagen stimulation, inflammation, and ECM remodeling. The GO, STRING, and Reactome analyses suggested that each has unique biological processes. PLLA-SCA stimulated more ECM components while inducing fewer inflammatory markers, allowing for morphogenesis, which is indicative of a regenerative pathway. Specifically, PLLA-SCA upregulated ELN, which encodes tropoelastin. This is significant because tropoelastin proteins attach to one another to form mature elastin. Elastin is the major component of elastic fibers, important for the tissue supporting connective tissue. ELN is only produced in a non-inflammatory environment. PLLA-SCA also induced MT1A expression, which codes for metallothionein-1A, an antioxidant that protects against hydroxyl free radicals. The impact of PLLA-SCA in increasing expression of DKK1, which regulates skin pigmentation and thickness by affecting Wnt/beta-catenin signaling in keratinocytes together with HGF, suggests a role in morphogenesis and a second pathway for regeneration. Previously published data has shown topical application of PLLA-SCA following fractional CO_2 laser re-pigmented atrophic scars, which may be explained by DKK1 upregulation.[11]

Beyond keratinocytes, the improved morphogenesis may impact other tissue types. The "morphogenic" descriptor was provided by the analytic software as the descriptive term encompassing the biological process. ELN, MMP2, and MMP10, unique in the PLLA-SCA group, are part of a local network cluster related to elastic fiber formation as established via the STRING analysis. Moreover, HGF identification suggests enrichment for the pluripotent stem cell differentiation pathway. The equivalent descriptor for the CaHA-R biological process was 'bone formation' due to MMP9 and PLAU (Plasminogen Activator, Urokinase), which is not surprising as CaHA is recognized as a part of bone development.

CaHA-R-induced gene upregulation showed enrichment associated with a pro-inflammatory response revolving around MMP9, a chronic inflammatory wound biomarker.[12] Other pro-inflammatory genes upregulated by CaHA-R include interferon alpha-1 (IFNA1), a cytokine that regulates immune function and mediates tissue inflammation and organ damage in several autoimmune diseases.[13] MMP9 and PLAU are also associated with an autoimmune inflammatory skin disease, as functional interactions were demonstrated between MMP9 and the plasminogen/plasmin system.[14]

Inflammation and regeneration are considered competitive entities, with regeneration taking place in a non-inflammatory milieu.[15] Previously reported data for CaHA-R has shown an increase in elastin following treatment.[16] However, those data were in non-facial areas and at much later time points than this study. These present data suggest that the location of injection may give rise to differential genetic profiles or that CaHA-R requires a longer timeline to shift from a pro-inflammatory state to an environment conducive to allowing ELN production.

The STRING database collects and integrates publicly available sources of protein-protein interaction information.[17] Interactions can be limited by cell types and physiological conditions and can vary by binding strength (obligatory, stable bindings or fleeting, unspecific encounters). Functional systems need protein-protein associations with informational flow biological interfaces that allow the flow of information through a cell to aid with functional implementation. The networks uncovered in STRING were used to filter and assess the data obtained from both study aspects. It provided information related to annotating the functional properties of genes that were significantly regulated in the groups. Gene ontology annotation is incorporated into the STRING analysis, providing information on terms that were over- or under-represented (including biological processes, molecular function, and cellular components).

The clinical results achieved in this study were in line with previously published data, with both treatments improving the depth and volume of NLFs.

Limitations of the study include a small sample size and limited gene assessments. Other limitations include the use of non-diluted CaHA-R. However, data predominately supports diluted and hyper-diluted CaHA-R for non-facial injections. Currently, United States FDA-approved facial indications for CaHA-R only include non-diluted injections.

To our knowledge, this is the first head-to-head comparison that assessed the genetic pathways of on-label facial injections for these two products. Previous studies compared non-facial injections, but the morphological differences between facial skin and body can vary.[20,21] Further research is needed to elucidate the earlier gene expression changes, long-term gene expression, protein production, and cellular morphological changes. Overall, this study identified novel, previously unknown genetic pathways for how PLLA-SCA and CaHA-R can induce collagen production via distinct gene upregulation. These data suggest a gene expression shift to regeneration due to a host response to PLLA-SCA, whereas CaHA-R has a gene expression signature of pro-inflammation and inflammation at 90 days.

DISCLOSURES

Dr Waibel has served as a consultant, advisor, speaker, or researcher for Allergan ArgenX, BellaMia, Bristol Myers Squibb, Candela, Cytrellis Biosystems, Eli Lilly, Galderma, Horizon, Incyte, Johnson and Johnson, Lumenis, Lutris, Olix Pharmaceuticals, Pfizer, P & G, RegenX, Sanofi, SkinCeuticals, Shanghi Biopharma, and VA Merit Grant; Dr Nguyen, Dr Le, Dr Ziegler, Dr Qureshi, Dr Widgerow, and Dr Meckfessel are employees of Galderma.

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ORIGINAL ARTICLE

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Utility of Adding Platelet-Rich Plasma to Microneedling vs Microneedling Alone in the Treatment of Acne Scarring

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ABSTRACT

Acne vulgaris is one of the most common skin diseases worldwide and affects a large population of patients. Post-acne scarring can pose a significant psychosocial burden on patients of all ages; therefore, treatment approaches must be both rapid-acting and effective. Microneedling is a minimally invasive technology that involves the creation of controlled tissue microinjury and subsequent induction of collagen production and tissue remodeling. Platelet-rich plasma (PRP) is an autologous preparation of plasma containing supraphysiologic concentrations of platelets, growth factors, and cytokines. The combination of microneedling and PRP therapy has been postulated to offer synergistic effects in the treatment of acne scarring. The purpose of this review is to critically analyze recent clinical trials that compare the efficacy of microneedling monotherapy to the combination of PRP and microneedling for the treatment of atrophic acne scarring.

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INTRODUCTION

Acne vulgaris is a very common cutaneous disorder with a multifactorial etiology. The development of acne vulgaris involves increased sebum production, follicular hyperkeratinization, *Cutibacterium acnes* colonization, and upregulated inflammatory responses.[1] The inflammatory destruction created by acne vulgaris can leave behind atrophic acne scarring, posing a significant negative psychosocial impact on patients.[1,2] Atrophic acne scarring can be classified into 3 main types: rolling, boxcar, and icepick scars. Patients can present with 1, 2, or all 3 scar types, therefore, an in-depth and nuanced evaluation of patients is imperative to pursue appropriate therapeutics.[1] Microneedling involves the creation of multiple microchannels within the skin that physically disrupt the dysregulated collagen bundles present within the superficial layer of the dermis of acne scars, and promotes the production of new collagen and elastin beneath the scars.[3] This controlled tissue microinjury triggers a cascade of wound healing events involving the release of multiple growth factors, including but not limited to platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor (TGF)- alpha and beta. Microneedling-induced fibroblast proliferation fosters the deposition of type 3, and ultimately type 1, collagen in an organized pattern.[3] There are multiple microneedling devices present on the market, which vary based on needle length, diameter, material, and quantity. The optimal parameters for microneedling have not been well defined and likely vary based on the targeted disease process.[3] Platelet-rich plasma (PRP) is an autologous preparation of plasma that contains a supraphysiologic concentration of platelets. Upon activation, the alpha-granules of platelets release high concentrations of growth factors such as TGF-β, PDGF, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and other chemokines and cytokines, which aid in cell differentiation, proliferation, and regeneration.[4] Thus, the combination of PRP and microneedling has been postulated to provide synergistic benefits to patients as the application of PRP following microneedling allows for deeper penetration of the agent and, thus, rapid-acting and effective treatment.

MATERIALS AND METHODS

A literature search was performed on PubMed in January 2024 using a combination of the keywords "platelet-rich plasma," "microneedling," "needling," "acne scarring," and "acne scar." We included published clinical trials from 2018 to January 2024, which included a comparison of the efficacy of combination PRP and microneedling and microneedling alone in more than 2 patients. In-vitro studies, animal trials, non-English articles, and studies that did not directly compare combination and monotherapy were excluded. Overall, 6 studies were rigorously reviewed and summarized (Table 1).

TABLE 1.

Summary of Study Characteristics

Study	Subjects	Study Design	Microneedling Device	PRP Preparation Protocol
Ibrahim et al[5]	N = 35 FST: I-IV	Split face comparative study Four sessions at 3-week intervals Right: microneedling monotherapy Left: microneedling followed by topical PRP Follow up: 3 months after the last session	Dermaroller with 192 needles 1500 µm in length	Double centrifugation 1. 2500 rpm for 10 min 2. 3500 rpm for 10 min Calcium gluconate was added to activate PRP (1:9)
Gupta et al[7]	N = 36	Split face comparative study Four sessions at monthly intervals Right: microneedling followed by topical PRP Left: microneedling monotherapy	Dermaroller with 192 needles 2.0 mm in length	Double centrifugation 1. 1400 rpm for 10 min 2. 3500 rpm for 10 min Calcium gluconate was added to activate PRP (1:9)
Nandini et al[9]	N = 30 FST: II-IV	Split face comparative study Four sessions at monthly intervals Right: microneedling followed by PRP application and intradermal injection Left: microneedling monotherapy Follow up: 6 months posttreatment	Roller drum with 192 needles 1.5 mm in length	Single centrifugation 1. 3600 rpm for 15 min
Elfar and Hasby[10]	N = 60 FST: II-IV	Single blinded randomized controlled study Four sessions at monthly intervals Group A: 20 patients were treated with intradermal injection of plasma gel only Group B: 20 patients were treated with microneedling monotherapy Group C: 20 patients were treated with topical plasma gel followed by microneedling, and additional plasma gel topical application Follow up: monthly for 3 months after the last treatment session	Dermaroller with 540 needles 2.0 mm in length	Double centrifugation 1. 72 g for 15 min 2. 1006 g for 5 min Syringes were placed in a hot water bath, then in a cold bath, each for 1 minute to create a viscous gel
Ismail et al[12]	N = 30 FST: III-V	Split face comparative study One session every 3 weeks until clearance of the atrophic acne scars or for four sessions maximally Group A: 15 patients Right: microneedling monotherapy Left: microneedling followed by topical PRP Group B: 15 patients Right: intradermal PRP Left: microneedling followed by topical PRP Follow up: 3 months after the last treatment session	Dermapen with 1.5 mm needles	Double centrifugation 1. 1000 rpm/m for 10 min 2. 1500 rpm/m for 10 min 3% calcium chloride was added to activate PRP (1:1.5)
Porwal et al[13]	N = 55 FST: III-V	Comparative study Three sessions at monthly intervals Group A: 28 patients treated with microneedling monotherapy Group B: 27 patients treated with intradermal PRP followed by microneedling Follow up: 1 month after the last treatment session	Dermaroller with 192 needles 1.5 mm in length	Double centrifugation 1. 1200 rpm for 15 min 2. 2000 rpm for 10 min

FST, Fitzpatrick skin type; PRP, platelet-rich plasma

RESULTS

Ibrahim et al[5] conducted a split-face, prospective clinical trial in which thirty-five patients received four sessions of microneedling followed by topical application of PRP on the left side of the face and microneedling alone on the right side of the face at 3-week intervals. A dermaroller with 192 titanium needles 1500 µm in length was used. Rolling was performed five times each in horizontal, vertical, and oblique directions. The treatment endpoint was characterized as uniform pinpoint bleeding. The final assessment of treatment was performed 3 months after the last session by two blinded dermatologists using photographs of patients before and after treatment, and the Goodman and Baron qualitative global acne scarring system.[6] Patient self-assessment scores were also used to characterize the perceived efficacy of treatment. Mean global acne scarring scores decreased significantly on the combination side (P<0.001) and the microneedling monotherapy side (P<0.001). However, there was no significant difference found between both treatments. Of note, the side receiving combination therapy experienced a significantly shortened duration of erythema and edema than that of the microneedling monotherapy side. Although this study did not ultimately reveal a significant clinical benefit of adjuvant PRP therapy with microneedling, it did prove the efficacy of both treatment approaches and offered a superior approach for patients who seek shorter downtime and less pronounced short-term side effects.

Gupta et al[7] performed a split-face study in which 36 patients were subjected to either microneedling alone or microneedling followed by topical PRP monthly for a total of four treatment sessions. A dermaroller with 192 needles 2.0 mm in length was used. Rolling was performed four times in each direction: horizontally, vertically, diagonally, right, and left. The treatment endpoint was characterized as uniform pinpoint bleeding. Acne scars were graded according to the échelle d'évaluation clinique des cicatrices d'acné (ECCA) grading system[8] at the first, second, fourth, and sixth visits, and a visual analog score (VAS) was also evaluated by physicians and patients at every visit. The investigators stratified patient scars by scar type: the most common scar type was boxcar scars, followed by icepick, then rolling scars. The mean percentage reduction of the total number of scars was 40% on the combination side and 37% on the microneedling monotherapy side, and the difference between the two was insignificant. The ECCA score decreased significantly on both sides after the second, fourth, and sixth visits. The mean ECCA score on combination and monotherapy sides decreased from 88.31 ± 32.78 to 62.92 ± 23.68 and from 89.58 ± 2.43 to 66.25 ± 23.89, respectively, with insignificant differences between the sides (P=0.058). Visual Analog Scale (VAS) evaluation by both patients and physicians showed improvement. However, the differences on both sides were not found to be statistically significant. Unlike the study by Ibrahim et al,[5] the authors of this study did not note a difference in side effect profile between the two treatment approaches. Interestingly, rolling scars were found to be most responsive to treatment, followed by boxcar scars, then icepick scars. Overall, this study found no significant additive benefit of the combination of PRP and microneedling therapy compared to microneedling monotherapy in the treatment of atrophic acne scarring. The authors note that the efficacy of PRP may be enhanced in future studies by observing the effects of occlusion following PRP application to maximize absorption as well as repetition of microneedling therapy after PRP application to increase penetration. Limitations of this study include small sample sizes and observer bias.

Nandini et al[9] conducted a split-face comparative study assessing the efficacy of microneedling alone versus microneedling combined with PRP. A roller drum with 192 needles 1.5 mm in length was used. Microneedling was performed in vertical, horizontal, and diagonal directions 4 to 5 times, after which PRP was applied topically and also injected intradermally on the right side only. Most patients presented with mixed boxcar and rolling-type acne scars. Patients were evaluated using the Goodman and Baron qualitative acne scar grading system.[6] Scars were assessed at the end of the 4 treatment sessions using digital photographs. Patients' perception of clinical response was assessed using the VAS. An overall decrease in scar severity was observed on the monotherapy side of 22 patients. In comparison, scars treated with combination therapy were observed to be reduced in 28 patients. The difference in number of patients having reduced scar severity for each scar type was not statistically significant, suggesting that these therapeutic approaches benefit several scar types. By physician assessment of the scar, an "excellent" response (improvement of two grades) was noted on the combination side of 43% of patients and the monotherapy side of 20% of patients. Greater than 75% improvement was reported by 3% of the patients on the monotherapy side as compared to 37% for the combination therapy side. Patient assessment scores were generally higher for the combination side as compared to the microneedling monotherapy side of the face. Although the authors of this study conclude that combination therapy is more effective than microneedling monotherapy, they do not note statistical significance when comparing the 2 treatment approaches. The lack of blinding in this study also increases the risk of bias and may affect perception levels and study outcomes. Although microneedling, both with and without PRP adjuvant therapy, appears to be an effective treatment for acne scarring, it is unclear whether the addition of PRP provides a significant synergistic benefit.

A single-blinded randomized controlled trial by Elfar and Hasby[10] evaluated 60 patients with atrophic acne scars. Patients were divided into three groups of twenty: treatment with intradermal plasma gel, treatment with microneedling,

and combination treatment with topical plasma gel and microneedling. A dermaroller (Micro Needle Roller System, ZGTS, Guangdong, China) with 540 needles 2.0 mm in length was used. Plasma gel was created by placing the PRP syringes into hot followed by cold water to produce a viscous gel. Patients in the combination treatment group received topical plasma gel followed by dermaroller and additional topical plasma gel application. Microneedling was performed eight times in multiple unspecified directions. The treatment endpoint was characterized as uniform pinpoint bleeding. Each group of patients received four sessions of treatment at monthly intervals. Goodman and Baron's quantitative scale was utilized to assess treatment response.[11] A pre-treatment score, 4-week score, and end-of-treatment session score were assigned. Histopathology and immunohistochemistry were conducted on 2-millimeter punch biopsies. There was a statistically significant difference in acne scar grades for patients treated with intradermal plasma gel at the one-month follow-up (P=0.027), but no statistically significant difference was found at the 3-month follow-up (P=0.204). As for the patients treated with microneedling, there was no significant difference observed between the pre-treatment, one-month, and 3-month follow-ups (P=0.121 and P=0.086, respectively). Patients receiving combination treatment had a statistically significant difference at one-month follow-up (P=0.041) and 3-month follow-up (P=0.016). Combination treatment showed a statistically significant difference in improvement of acne scar grading compared to the intradermal plasma gel group by 3 months after the last treatment session (P=0.009). Regarding the degree of clinical improvement, 3 months after the last treatment session, the combination therapy group showed significantly better improvement than the plasma gel monotherapy group (P=0.040), while the plasma gel monotherapy group failed to show superior results to the microneedling cohort. Boxcar and rolling scars showed the greatest improvement. Microneedling patients reported the most erythema and pain. Similarly to Ibrahim et al, the addition of topical plasma gel improved recovery time when compared to microneedling alone. After treatment, histopathology showed more condensed and organized dermal collagen and a decrease in perivascular inflammatory cell infiltrates across groups. In conclusion, plasma gel was found to augment microneedling therapy in the treatment of atrophic acne scars, with individual intradermal plasma gel and microneedling therapy also showing positive results. It is possible that the gel formulation of PRP enhanced treatment outcomes by providing an immediate filling effect.

Ismail et al[12] assessed microneedling and PRP alone and in combination for the treatment of atrophic acne scars in a prospective, randomized, comparative split-face trial. Thirty patients were randomized to two treatment arms. Group A received microneedling alone on the right side of their face and microneedling followed by topical PRP on the left side of their face. Group B received intradermal PRP on the right side of their face and microneedling followed by topical PRP on the left side of their face. A dermapen (MY M, Korea) with needle lengths of 1.5 mm was used. The technique of rolling was not specified. The treatment endpoint was characterized as uniform pinpoint bleeding. Treatment was repeated every 3 weeks in both groups until clearance of scars or maximally for 4 weeks. Digital photographs were obtained pre-treatment, before each session, and one month after the last session. Images were evaluated by 2 dermatologists using a quartile grading system, the Goodman and Baron qualitative grading system,[6] and the ECCA scale.[8] Patient satisfaction was also obtained using a quartile grading system. In group A, microneedling with topical PRP showed a higher percentage of marked and excellent improvement on a quartile scale compared to microneedling alone, but the difference was not statistically significant (P=0.701). There was also greater improvement in the combination side based on the Goodman and Baron scale, but the difference did not reach statistical significance (P=0.104). This was further supported using the ECCA scale, where the combination treatment side in group A showed 26.7% good (51-75%) and 6.7% excellent (>75%) improvement, compared to 20% good and 0% excellent improvement with microneedling alone; nevertheless, this was not statistically significant (P=0.599). Both sides of the face saw improvements in the treatment of both icepick and rolling scars. Interestingly, microneedling was found to have better results for patients with a shorter scar duration, while combination treatment showed a non-significant negative correlation between the percentage of improvement of scars and duration of scars, indicating a potential benefit of combination treatment for longstanding scars. In group B, microneedling and topical PRP combination showed statistically significant higher percentages of excellent (26.7%) or marked improvement (40%) compared to intradermal PRP, where 0% and 13.3% of patients achieved excellent and marked responses, respectively. The Goodman and Baron scale identified greater improvement on the microneedling and topical PRP combination side compared to the right side, without statistical significance. The ECCA scale identified superior improvement on the side treated with the combination of microneedling and topical PRP compared to intradermal PRP alone. Specifically, statistically significant differences were noted in the combination treatment of icepick and rolling scars. Notably, microneedling and topical PRP combination, as well as intradermal PRP alone, had a statistically significant reduction in scars but with better results in the combination treatment group. There was also a statistically significant increase in patient satisfaction in the combination treatment group (P=0.002). Altogether, the study supports a combined treatment approach with both microneedling and PRP for optimal outcomes in the treatment of atrophic acne scars; nevertheless, microneedling and PRP monotherapy have also shown effective results.

Porwal et al[13] conducted a comparative study looking at the differences in outcomes of facial acne scars and quality of life before and after treatment with combined microneedling and PRP versus microneedling alone. Fifty-five patients were included, of which 28 were assigned treatment with microneedling alone, and 27 were assigned combination treatment with intradermal PRP injections followed by microneedling treatment. A dermaroller with 192 microneedles 1.5 mm in length was used. Microneedling was performed in horizontal, vertical, and diagonal directions. The treatment endpoint was characterized as uniform pinpoint bleeding. Patients were treated at monthly intervals for a total of 3 sessions. A final analysis was conducted one month after the final session. Outcomes were assessed using the Goodman and Baron's quantitative scale[11] and the dermatology life quality index score (DLQI), a questionnaire assessing health-related quality of life in patients with dermatologic conditions.[14] Both groups saw improvements in their acne scars, with a 43.03% improvement observed in those receiving microneedling alone and a 58.58% improvement in those treated with microneedling and PRP injections on the Goodman and Baron's scale. A statistically significant difference was found between groups (P<0.05). Following treatment, the DLQI scores showed a 42.67% improvement in patients receiving microneedling alone and a 58.47% improvement in patients treated with a combination of microneedling and PRP injections. A statistically significant difference was noted between groups (P<0.001). Overall, the study found microneedling to be effective in the treatment of acne scars, with the addition of PRP injections further enhancing outcomes.

CONCLUSION

Atrophic acne scarring is a complex disease process, the foundation of which involves the dysregulation of collagen during wound healing. Microneedling involves the creation of controlled tissue microinjury, which, when combined with topical treatments, may allow for enhanced drug delivery and efficacy. Given the potential for synergistic effects with combination therapy, the purpose of this review was to analyze recent clinical trials investigating the combination of PRP and microneedling for the treatment of acne scarring (Table 1). There is currently no consensus on a universal treatment protocol for acne scarring, and optimal therapy likely involves a multimodal approach. While the studies in this review showed improved acne scarring with combination treatment, not all studies found significant differences when compared to monotherapy. While there appears to be no serious consequences associated with adjunct PRP therapy, the variability in support for the additional benefit of combination therapy should be discussed with patients since the incorporation of PRP may pose an additional economic burden.

The synergistic effects of PRP and microneedling are thought to be caused by enhanced PRP absorption and efficacy through the microchannels and tissue injury milieu created by microneedling. This may explain improved post-procedure edema and erythema in combined microneedling and PRP-treated patients.[5] The mechanism of improved edema and erythema is likely due to the tissue regeneration promoting growth factors within PRP, which enhance healing following physical injury, decreasing the duration of post-procedure inflammation and thus decreasing recovery time.[5] However, this finding was not consistent across all studies reviewed, suggesting the need for future trials investigating PRP as an adjunct therapy to abrasive treatment.

Histopathologic evidence of the efficacy of combination treatment includes increased and more organized collagen fiber deposition post-treatment.[10] Furthermore, with combination therapy, new collagen bundles are deposited in a normal lattice pattern rather than in parallel, the pattern typically observed in scar tissue.[15] Histopathologic evidence serves as an objective method for evaluating treatment response and should be incorporated in future studies to contextualize the correlation between observed clinical efficacy and pathologic results.

An overarching limitation identified during this critical review was the presence of variabilities in PRP protocols. Factors that may affect PRP potency and efficacy include but are not limited to, type of anticoagulant, centrifugation protocol, red blood cell count, platelet count, leukocyte count, and platelet activation.[16] Given the potential clinical implications of PRP treatment protocol variations, any study using PRP should clearly outline preparation and administration procedures. Although there is currently no consensus on an optimal regimen, as PRP becomes a more popular treatment for acne scarring, future clinical trials may require more rigorous protocol standardization.

DISCLOSURES

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

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Expert Roundtable on Skin Care Integration After Aesthetic Procedures: Consensus Recommendations

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ABSTRACT

Currently, available technologies and procedures enable aesthetic dermatologists to provide their patients with beneficial treatment outcomes for a wide variety of skin conditions. These treatments range from laser resurfacing and radiofrequency procedures to chemical peels and microneedling. The concept of integrated skincare is based on the application of adjunct therapies before, during, or after cosmetic medical procedures to promote healing, minimize discomfort, shorten down-time, and enhance overall aesthetic outcomes. Numerous peer-reviewed studies have demonstrated the benefit of combining a variety of adjunct treatments with cosmetic procedures. The concurrent application of integrated skincare can improve these skin-related issues and provide patients with greater global outcomes. The primary objective of the following consensus roundtable was to discuss best practices for aesthetic providers with or without dermatological training when treating patients with aging skin complaints and review considerations for evaluating patients interested in cosmetic procedures with concomitant skin issues, such as skin dyschromias, lines, and wrinkles. A roundtable discussion was held by several notable experts in their field during a special addition to the Thriving in Diversity webinar series on Saturday, July 8, 2023. The discussion included four leading dermatologists, one oculoplastic surgeon, and one facial plastic surgeon who provided their clinical experience and consensus recommendations for applying integrated skincare in the aesthetic medical practice.

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INTRODUCTION

Integrated Skincare

Numerous technologies and procedures are currently available to aesthetic dermatologists, enabling them to provide beneficial outcomes to their patients for a wide variety of conditions. Existing noninvasive treatments range from laser resurfacing and radiofrequency procedures to microneedling and chemical peels. Many patients presenting for aesthetic treatments may have concomitant skin disorders, such as acne vulgaris, rosacea, or melasma. In one study, the prevalence of acne among women was 50.9% for those aged 20 to 29 years, 35.2% for those aged 30 to 39 years, 26.3% for those aged 40 to 49 years, and 15.3% for those aged 50 years or older.[1]

The concept of integrated skincare is the application of adjunct therapies to promote healing, minimize discomfort, shorten down-time, and enhance overall aesthetic outcomes. Numerous peer-reviewed studies have demonstrated the benefit of combining a variety of agents before, during, and after cosmetic procedures. The concurrent application of integrated skincare can improve these skin-related issues to provide patients with greater global outcomes.

The primary objective of this consensus roundtable was to discuss best practices for aesthetic providers with or without dermatological training when treating patients with common aging skin complaints in an aesthetic clinic and review considerations for evaluating patients interested in cosmetic procedures with concomitant skin issues, such as acne, skin dyschromias, lines, and wrinkles.

MATERIALS AND METHODS

A roundtable discussion was held by six notable experts in their field during a special addition to the Thriving in Diversity webinar series on Saturday, July 8, 2023.[2] Four expert dermatologists, one oculoplastic surgeon, and one facial plastic

surgeon provided their clinical experience and consensus recommendations for applying integrated skincare into the aesthetic medical practice. Four presenters were provided an opportunity to share knowledge while the other experts and the viewing audience responded with questions. This activity was planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of FabDay LLC and Global Education Group, which is accredited by ACCME to provide continuing medical education for physicians.

DISCUSSION

Integrating Skincare With Injectable Fillers, Biostimulators, and Devices for Anti-Aging

Integrated skincare is an important concept when treating patients with injectables and devices for treating lines, wrinkles, and other age-related effects to achieve maximally beneficial results and to reduce the risks of infection, scarring, and hyperpigmentation. These include neuromodulators, hyaluronic acid fillers, biostimulators, intense pulsed light (IPL), broadband light (BBL), and ablative and non-ablative lasers. As patients may have spent a great deal of money to achieve their desired aesthetic effects, integrated skincare is an important means for protecting their investment. Several studies have demonstrated the benefit of peri- and post-non-surgical aesthetic treatment adjunctive care.

Topical skin care is an important component of office-based aesthetic treatments. It can optimize cosmetic outcomes on the face and other anatomical areas and engage patients in their self-care. Also, it likely primes patients for attentive skin care in the future.

In one split-face study, for example, subjects applied a bland moisturizer or a tripeptide/hexapeptide serum (TriHex Technology®; Alastin Skincare®, Inc.) to one side of their face twice daily for 14 days prior to 2 nonablative fractional resurfacing procedures 1 month apart and continuing for 60 days afterward.[3] The areas treated with the tripeptide/hexapeptide serum showed greater improvements for nearly all outcome measures, including modified Melasma Area Severity Index[4] (mMASI) scores. Use of the same product technology 2 weeks prior and 1 week following a single radiofrequency microneedling procedure (Intensif, Endymed™; 3Deep Skin Science). In one study, the prevalence of acne among women was 50.9% for those aged 20 to 29 years, 35.2% for those aged 30 to 39 years, 26.3% for those aged 40 to 49 years, and 15.3% for those aged 50 years or older.).[5] After 90 days, the tripeptide/hexapeptide serum-treated subjects showed improved neocollagenesis and elastogenesis, decreased erythema, enhanced healing, and overall outcomes.[6]

A randomized, double-blind clinical trial treated subjects with mild-to-moderate skin laxity on the posterior thighs and buttocks with 2 monthly radiofrequency microneedling procedures.[7] Subjects randomly applied a topical skin-tightening agent (Body Tightening Concentrate; SkinCeuticals) to one leg twice daily for 8 weeks. While both areas showed improvement, it was significantly greater for the area treated with the topical agent.

One webinar presenter suggested a basic post-treatment skin regimen for an anti-aging intervention should always include an antioxidant and a mineral-based sunscreen in the morning and a topical retinol and moisturizer in the evening. Antioxidants are compounds that neutralize free radicals, highly unstable molecules with unpaired electrons whose cascade effect can damage or destroy collagen, elastin, and DNA. Beneficial effects of antioxidants include substantial protection from solar radiation,[8] decreased ultraviolet (UV)-induced sunburn cell formation, and decreased thymine dimer formation associated with skin cancer development.[9,10] Antioxidants should be the first part of the skincare regimen after cleansing and drying the face in the morning.

Silymarin, or milk thistle, derived from the plant *Silybum marianum*, has demonstrated numerous antioxidant properties,[11] while L-ascorbic acid plays a critical role in promoting collagen synthesis and wound healing. When topically administered, a blend of L-ascorbic acid as a serum, silymarin, and salicylic acid has demonstrated visible reductions in skin oiliness, refined skin texture, improved skin clarity, fine lines, and overall skin appearance[12] (Silymarin C F™; SkinCeuticals). Prior treatment with a 1,440-nm laser (Clear + Brilliant® Laser System; Solta Medical, Bothell, WA) has been shown to enhance skin uptake of L-ascorbic acid (specific products not named) by approximately 10- to 20-fold.[13] Five drops of serum can be applied to the face and neck before adding other topicals post-laser treatment. For normal-to-dry skin, a product containing 15% L-ascorbic acid and 0.5% ferulic acid serves as a good antioxidant for moisturizing the skin (C E Ferulic® with 15% L-ascorbic acid; SkinCeuticals).

The use of sunscreens is essential to protect newly rejuvenated skin and prevent further sun damage. Preferred sunscreens are mineral-based, containing zinc oxide and titanium dioxide to provide total ultraviolet A (UVA)/ultraviolet B (UVB) protection.[14] To prevent a chalky appearance, some mineral sunscreens are formulated with iron oxide for a more natural appearance and enhanced skin protection (Sunforgettable Total Protection®; Colorscience, Inc.).[15] It is recommended that patients be counseled on sunscreen application as studies have shown that patients often fail to apply proper protection to such areas as the hairline, ears, and neck.[16]

The use of retinoids has long been shown to promote skin healing after dermal procedures. In one study, male subjects with actinically damaged skin were treated daily with 0.1% tretinoin (Retin-A® Cream; Ortho Dermatologics) and placebo creams to the left and right halves of the face for 14 days prior to the 35% TCA peel.[17] Healing occurred significantly sooner in skin pretreated with tretinoin. After 7 days, 75% of the tretinoin-pretreated areas were completely healed versus 31% of placebo-pretreated areas. Similar results were reported for the arms and hands.

Based on a literature search and personal experience, an algorithm for the pre-procedure use of tretinoin in facial resurfacing has been developed.[18] For ablative lasers, apply 0.1% tretinoin cream nightly for 3 months prior to the planned procedure and discontinue 24 hours prior. For non-ablative laser resurfacing, decrease the dose to 0.05%. Tretinoin pretreatment is not recommended for microdermabrasion as the procedure only affects the superficial epidermis. Pretreatment with 0.1% tretinoin cream is recommended for surgical dermabrasion starting 3 months prior to the planned procedure.

For chemical peel resurfacing, tretinoin pretreatment recommendations depend on the depth of the peel.[18] For superficial chemical peels, use a 0.05% product daily starting 1 month prior to the procedure, stopping 24 hours before the treatment. For medium chemical peels, use 0.1% daily starting 1 month prior to the procedure and stopping 24 hours prior to the procedure. For deep chemical peels, use 0.1% tretinoin daily, starting 3 months prior to the procedure and stopping 24 hours prior. Of note, there is no apparent benefit on scar formation from applying vitamin E after skin surgery.[19]

Moisturizers may be applied to enhance the tolerability of retinol. The choice of moisturizer can be left to personal preference, and over-the-counter products are acceptable but dependent on skin type. If skin is oily and noncomedogenic, oil-free-based moisturizers can be used. If drier, post-menopausal, non-acneiform skin is being treated, lipid-containing moisturizers, such as ceramide- or dimethicone-based moisturizers, can be used.

Melasma and Hyperpigmentation

Melasma is a common acquired hyperpigmentation disorder that most frequently occurs among women with Fitzpatrick skin types III to VI and with a mean age of onset between 20 to 30 years. The clinical pattern in up to 80% of cases is centrofacial, affecting the forehead, nose, upper lip, cheeks, and chin.[20] This condition has a significant impact on the quality of life and self-esteem of affected individuals.[21]

Historically, melasma has been a difficult condition to treat due to a high rate of recurrence. Topical hydroquinone has long been the gold standard for treating melasma. It inhibits the conversion of dihydroxyphenylalanine (DOPA) to melanin and is involved in degrading melanosomes and melanocytes.[22] In one placebo-controlled study, topical 4% hydroquinone-treated subjects achieved a 72% improvement in melasma compared to placebo[23]; however, adverse events may include irritation, erythema, and pruritus. Long-term use of hydroquinone is associated with ochronosis, a blue-black cutaneous hyperpigmentation.[22]

Although uncommon, the potential for ochronosis prompted the United States Food and Drug Administration (FDA) to ban the sale of over-the-counter hydroquinone products >2% strength in 2020.[24] Currently, the only FDA-approved hydroquinone-containing product is indicated for the short-term treatment of moderate-to-severe facial melasma and should only be used under the supervision of a licensed health care professional (Tri-Luma® Cream; Galderma Laboratories).[25] Other available treatments for melasma include topical and oral tranexamic acid, cysteamine, azelaic acid, topical metformin, methimazole, platelet-rich plasma, botanicals (*Rumex occidentalis*), and superficial chemical peeling.[22,26,27]

Numerous studies have compared the efficacy of these compounds with hydroquinone. An open-label study compared the effect of 20% azelaic acid and 4% hydroquinone cream applied twice daily for treating melasma (product names not specified).[28] All subjects used a broad-spectrum sunscreen. Improvement in the azelaic acid-treated group became significantly greater than hydroquinone after 2 months. A recent systematic review compared azelaic acid 20% and hydroquinone 2 to 4% for treating melasma found azelaic acid may be superior to hydroquinone while acknowledging larger studies with long-term follow up are needed.[29]

Similarly, treatment with topical tranexamic acid appears to be only slightly superior to topical hydroquinone[30]; however, the efficacy of tranexamic acid is greatly increased when combined with microneedling. A prospective, randomized, open-label study with a split face design combined microneedling with 10% tranexamic acid (product name not specified) on one side versus microneedling with placebo on the other side.[31] Four treatments were applied at 2-week intervals. The tranexamic acid-treated side achieved a 65.92% improvement in mean melasma severity scores versus 20.75% on the side with microneedling alone. Similar results have been reported by other investigators.[32] Tranexamic acid can also be combined with lasers for refractory melasma.[33] Topical agents used for treating melasma are summarized in Table 1.

Although the pathophysiology of melasma is multifactorial, ultraviolet light can significantly worsen the condition.[34] Consequently, cases of melasma are likely to be resistant or to relapse unless strict sun protection is maintained. Mineral

TABLE 1.

Topical Agents for Treating Hyperpigmentation	
Topical Agents	**Mechanism of Action**
Azelaic acid	Competitively inhibits tyrosinase and blocks reactive oxygen species in the melanogenesis pathway.[22]
Bakuchiol	Appears to target cellular pathways similar to retinol.[66,67]
Corticosteroids	Blocks UV-B-induced melanogenesis by prostaglandin and cytokine inhibition.[22]
Cysteamine	Inhibits tyrosinase activity and decreases melanocyte function.[22]
Glycolic acid (alpha-hydroxy acid)	Causes desquamation by reducing skin cell adhesion and suppresses tyrosinase activity and melanin synthesis.[22]
Hydroquinone	Inhibits tyrosinase and the conversion of DOPA to melanin and degrades melanosomes and melanocytes.[22]
Kojic acid	Inhibits tyrosinase activity by chelating divalentions.[22]
Licorice	Melanogenesis inhibition occurs through the degradation of microphthalmia-associated transcription factor via activation of the extracellular signal-regulated protein kinase signaling pathway and suppression of tyrosinase expression.[68]
Salicylic acid	Keratolytic and anti-inflammatory.[22]
Silymarin	Inhibits melanin synthesis, probably by blocking tyrosinase activity.[69]
Tranexamic acid	Not known with certainty but may inhibit melanin synthesis by inhibiting melanocyte/ keratinocyte interactions. It may also reverse other changes associated with melasma such as increased dermal vascularity and angiogenic factor expression.[22]
Tretinoin	By inhibiting tyrosinase, decreases melanin transfer and increases keratinocyte turnover.[22]
L-Ascorbic acid (Vitamin C)	Inhibits tyrosinase by binding to copper blocking melanin production in the melanogenesis pathway.[22]

sunscreens are highly effective for blocking ultraviolet radiation, high-energy visible light, and infrared radiation.[35] Sunscreens tinted with iron oxides further increase protection against visible light and UVA radiation.[15]

Some mineral sunscreens are available in a range of colors to match darker skin tones (Tint Du Soleil®; Colorscience, Inc.). A combination of topical 2% phloretin, 10% L-ascorbic acid, 0.5% ferulic acid may provide synergistic protection when used with sunscreens[10] (Phloretin CF® with Ferulic Acid; SkinCeuticals). Patients should be counseled that photoprotection also includes minimizing midday sun exposure and seeking shade, wearing wide-brimmed hats, photoprotective clothing, and sunglasses.[36]

Acne and Acne Scarring

Acne is among the most common skin disorders treated by dermatologists.[37] As noted above, acne often affects women at an age when they may be seeking treatment for other age-related conditions, such as facial lines and wrinkles.[38] The influence of social media has increased the acceptance of cosmetic procedure among younger individuals.[39]

Topical retinoids are a mainstay for treating acne but may cause tolerability issues due to skin dryness. Concomitant use of a lipid moisturizer containing 2% ceramide, 4% cholesterol, and 2% fatty acids (Triple Lipid Restore 2:4:2; SkinCeuticals) can decrease skin dryness, shorten the retinoid adjustment period, and improve overall tolerability of retinoids.

Chemical peels and lasers are also often used for treating acne. Chemical peels can minimize comedones and also post-inflammatory hyperpigmentation (PIH) from comedonal or inflammatory acne.[2] Energy-based technologies, such as pulsed dye laser and intense pulsed light have been shown to decrease active inflammatory acne. Photodynamic therapy using a photosensitizer, such as 10% or 20% 5-aminolevulinic acid, and activation with red or blue light and laser devices has shown efficacy in treating acne. A product containing 0.5% silymarin, 15%L-ascorbic acid, 0.5% ferulic acid, and 0.5% salicylic acid (Silymarin CF®; SkinCeuticals) may help with the treatment of active acne because of the salicylic acid component, while preventing and/or treating the occurrence of PIH with the use of 0.5% silymarin. A noncomedogenic, oil-free mineral-based sunblock is advisable to prevent the worsening of post-inflammatory erythema and the onset of PIH.

Ablative and non-ablative lasers can reduce acne scarring and PIH, depending on the Fitzpatrick skin type. The use of topical L-acetic acid, vitamin E, and 0.5% ferulic acid (C E Ferulic®; SkinCeuticals) can decrease treatment-associated erythema and increases fibroblast growth factor to speed wound healing following fractional ablative CO_2 laser therapy.[40,41] Again, a noncomedogenic, oil-free mineral-based sunblock to minimize post-inflammatory erythema and onset of post-inflammatory hyperpigmentation is advisable.

TABLE 2.

Cosmeceutical Agents for Treating Rosacea		
Agents	**Actives**	**Skin Function**
Green Tea	Polyphenols	Antioxidant, reduces ultraviolet B (UVB)-induced inflammation
Aloe vera	Aloin, aletinic acid	Inhibits cyclooxygenase pathway
Resveratrol	Polyphenols	Antioxidant/antiinflammatory
Tanacetum parthenium (feverfew)	Parthenolide, tanetin	Antioxidant, inhibits prostaglandin (Pg) release
Glycyrrhiza inflata (licorice)	Licochalcone A	Inhibits Pg release in response to UVB radiation

From: Draelos ZD. Rosacea and skin care, 2023. Available: https://www.zoedraelos.com/articles/rosacea-and-skin-care/. Accessed: July 25, 2023.

Facial Redness and Rosacea

Causes of facial redness include rosacea, acne, photodamage, post-inflammatory erythema, and other inflammatory skin disorders.[42] Rosacea is a common, chronic cutaneous disorder primarily affecting the convexities of the central face. Rosacea may be associated with intermittent or continuous flushing or erythema, papules, pustules, and telangiectasia.[43] A systematic review of available studies reported a prevalence of 5.46% among the general population, with a higher prevalence among northern Europeans.[44] It affects women more than men (5.41% vs 3.90%).[45] Rosacea has demonstrated a significant negative impact on quality of life.[46]

A list of approved products for the treatment of rosacea is available from the National Rosacea Society.[47] These include a range of topical products including azelaic acid (Finacea®),[48] encapsulated benzoyl peroxide (Epsolay®),[49] brimonidine (Mirvaso®),[50] ivermectin (Soolantra™),[51] oxymetazoline (Rhofade®),[52] minocycline (Zilxi®),[53] and metronidazole (Noritate®). Systemic medications include minocycline (Oracea®) and energy-based therapies include intense pulsed light (IPL), pulsed dye, and other laser devices.[54-56]

Numerous other treatments are available for skin redness. L-ascorbic acid, the active form of vitamin C, has significant antioxidant and anti-inflammatory properties[57]; however, it is an unstable molecule and must be specifically formulated with respect to pH and stabilizers such as alpha-tocopherol and ferulic acid. A topical mixture of vitamins C and E stabilized by ferulic acid was shown to protect the skin against erythema caused by ultraviolet radiation.[58]

Another useful antioxidant/anti-inflammatory agent is azelaic acid which has shown benefit for treating erythema due to rosacea and acne.[59] Niacinamide, a form of vitamin B_3, is photoprotective and improves skin barrier function by promoting ceramide synthesis. Niacinamide is widely used in sunscreens and moisturizers and has been shown to improve rosacea symptoms.[60] Numerous cosmeceuticals that are beneficial for treating redness associated with rosacea are summarized in Table 2.[61]

Many over-the-counter products can also provide *Integrative Skincare*. A dermatology consensus panel concluded moisturizers and cleansers providing hydration, correct skin pH, restore the microbiome, and provide skin lipids help improve the signs and symptoms of rosacea.[62] Specifically, occlusives and humectants, and product that provide ceramides, hyaluronic acid, and niacinamide are beneficial.

Combining the principles of integrative skincare, one study examined the benefits of IPL for treating patients with rosacea.[63] Subjects with moderate or severe rosacea received a single session of IPL on both sides of their face (540 nm, pulse duration 15 ms, pulse train 10, 30 J/cm^2). Immediately afterward, a mask containing botanical extracts, a calming dipeptide, and hyaluronic acid was applied to the right side of the face for 15 minutes (Phyto Corrective Masque; SkinCeuticals). The right side of each subject was also treated with a hyaluronic acid serum twice daily (Phyto Corrective Gel; SkinCeuticals), an antioxidant nightly (Resveratrol B E; SkinCeuticals), and the Phyto Corrective Mask was repeated once-weekly. All subjects applied sunscreen to both sides of the face (Sheer Physical UV Defense SPF 50; SkinCeuticals). Subjects were evaluated on posttreatment day 1 and after 1 and 3 months.

After 3 months, all rosacea symptoms were absent or mild, and the mean Rosacea Symptom Severity score decreased from 2.7 to 0.6. Mean physician Global Aesthetic Improvement Scale (GAIS) scores improved on both sides of the face following IPL but were greater on the right side. GAIS scores also showed that 40% of subjects achieved immediate improvement on the right side of the face versus 30% on the left side. All subjects (100%) achieved less skin redness, improved skin hydration, and overall better skin appearance on the right side of the face.

Exosomes derived from human platelet extract may facilitate skin rejuvenation[64]; however, this therapy remains experimental and has not been proven efficacious for facial redness.[65]

CONCLUSION

For patients seeking treatment for aged and photodamaged skin, melasma and hyperpigmentation, acne, and rosacea, employing the concept of integrated skincare before, during, or after cosmetic medical procedures can promote healing, minimize discomfort, shorten downtime, enhance global aesthetic outcomes, and deliver greater patient satisfaction.

DISCLOSURES

Sabrina Fabi MD has received consulting fees from AbbVie, Inc., Galderma, Merz Aesthetics®, Revance Therapeutics, Inc., Endo Pharmaceuticals, Croma Pharma®, L'Oreal Groupe, Ortho Dermatologics, and RoC® Skincare; is on the speaker's bureau for AbbVie, Inc., Galderma, and Merz Aesthetics®, and has received grants or research support from AbbVie, Inc., Galderma, Merz Aesthetics®, Symatese Aesthetics, Endo Pharmaceuticals, Croma Pharma®, Teoxane, and Raziel Therapeutics; and is a stockholder in Allergan Aesthetics, and Revance Therapeutics. Julie Woodward MD has received consulting fees from Allergan Aesthetics, Galderma, Prollenium Medical Technologies, Tarsus Pharmaceuticals, and Horizon Therapeutics; is on the speaker's bureau for Allergan Aesthetics, Galderma, Prollenium Medical Technologies, and SkinCeuticals; and holds stock options for Stroma Medical Corporation. Mara Weinstein Velez MD has received consulting fees from Allergan Aesthetics, Merz Aesthetics, Galderma, and Sofwave™. Steven Dayan MD is a consultant to Allergan Aesthetics, Galderma, Merz Aesthetics®, Evolus, Inc., and Endo Pharmaceuticals; is on the speaker's bureau for Allergan Aesthetics, Galderma, and Merz Aesthetics®; and has received grants and research support from Allergan Aesthetics, Galderma, Merz Aesthetics®, Teoxane, Endo Pharmaceuticals, and Croma Pharma®. Monica Boen MD has received consulting fees from SkinCeuticals and performed contract research for Eirion Therapeutics, Inc., SkinCeuticals, Biofrontera, Inc., Abbvie, Inc., and Galderma. Andrea Hui Austin MD is a consultant to Galderma, Allergan Aesthetics, and Merz Aesthetics.

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Physician Accreditation Statement

This activity was planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Global Education Group (Global) and FabDay LLC. Global is accredited by the ACCME to provide continuing medical education for physicians.

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FOR THE TREATMENT OF ACNE VULGARIS IN PATIENTS 12 YEARS OF AGE AND OLDER[1]

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(clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%

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The *first and only* FDA-approved, fixed-dose triple-combination topical prescription for the treatment of acne[2]

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INDICATION

CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1% is indicated for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

CABTREO is contraindicated in patients with:

- known hypersensitivity to clindamycin, adapalene, benzoyl peroxide, any components of the formulation, or lincomycin.
- history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported. If a serious hypersensitivity reaction occurs, discontinue CABTREO immediately and initiate appropriate therapy.

Colitis: Clindamycin can cause severe colitis, which may result in death. Discontinue CABTREO if diarrhea occurs.

Photosensitivity: CABTREO may increase sensitivity to ultraviolet light. Avoid or minimize exposure to sunlight and sunlamps. Wear sunscreen and protective clothing when sun exposure cannot be avoided.

Skin Irritation and Allergic Contact Dermatitis: Stinging/burning/pain, erythema, dryness, irritation, exfoliation, and dermatitis may occur with use of CABTREO and may necessitate discontinuation. Weather extremes, such as wind or cold, may be irritating to patients under treatment with CABTREO. Depending upon severity, patients can use a moisturizer, reduce frequency of application, or discontinue use. Avoid applying CABTREO to areas of broken, eczematous, or sunburned skin, and concomitant use with other potentially irritating topical products. Avoid use of "waxing" as a depilatory method on skin treated with CABTREO.

Use of CABTREO with concomitant topical acne therapy has not been evaluated.

ADVERSE REACTIONS

The most common adverse reactions (occurring in >1% of the CABTREO group and greater than the vehicle group) were application site reactions, pain, erythema, dryness, irritation, exfoliation, and dermatitis.

DRUG INTERACTIONS

Use CABTREO with caution in patients receiving neuromuscular blocking agents.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on adjacent pages.

References: 1. CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1% [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Stein Gold L, Baldwin H, Kircik LH, et al. Efficacy and safety of a fixed-dose clindamycin phosphate 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% gel for moderate-to-severe acne: a randomized phase II study of the first triple-combination drug. *Am J Clin Dermatol.* 2022;23(1):93-104. **3.** Stein Gold L, Lain E, Del Rosso JQ, et al. Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel for moderate-to-severe acne: Efficacy and safety results from two randomized phase 3 trials. *J Am Acad Dermatol.* 2023;89(5):927-935.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION This Brief Summary does not include all the information needed to use CABTREO safely and effectively. See full prescribing information for CABTREO.

CABTREO™ (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%
Initial U.S. Approval: 2023

INDICATION

CABTREO (clindamycin phosphate/adapalene/benzoyl peroxide) Topical Gel, 1.2%/0.15%/3.1% is indicated for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
CABTREO is contraindicated in patients with:

- Known hypersensitivity to clindamycin, adapalene, benzoyl peroxide, any other components of CABTREO, or lincomycin.
- A history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Hypersensitivity
Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported with use of clindamycin phosphate, benzoyl peroxide, and adapalene. If a serious hypersensitivity reaction occurs, discontinue CABTREO immediately and initiate appropriate therapy.

Colitis
Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical and systemic clindamycin. Severe colitis has occurred with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death. Discontinue CABTREO if diarrhea occurs.

Photosensitivity
CABTREO may increase sensitivity to ultraviolet light. Avoid or minimize sun exposure (including use of tanning beds, and sun lamps) following CABTREO application. Instruct patients to use sunscreen products and wear protective apparel (e.g., hat) when exposure to sun cannot be avoided.

Skin Irritation and Allergic Contact Dermatitis
Stinging/burning/pain, erythema, dryness, irritation, exfoliation, and dermatitis have been reported with use of CABTREO. These application site adverse reactions occurred at a greater frequency in CABTREO-treated subjects than in vehicle-treated subjects. These adverse reactions are most likely to occur during the first four weeks of treatment. Irritant and allergic contact dermatitis have been reported with use of CABTREO. Weather extremes, such as wind or cold, may be irritating to patients under treatment with CABTREO. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of CABTREO, or discontinue use. Avoid applying CABTREO to areas of broken, eczematous, or sunburned skin. Avoid use of "waxing" as a depilatory method on skin treated with CABTREO. Avoid concomitant use of other potentially irritating topical products such as peeling, desquamating, or abrasive agents and products with high concentrations of alcohol, astringents, spices, or limes. Use of CABTREO with concomitant topical acne therapy has not been evaluated.

ADVERSE REACTIONS
The most common adverse reactions (occurring in >1% of the CABTREO group and greater than the vehicle group) were application site reactions, pain, erythema, dryness, irritation, exfoliation, and dermatitis.

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
In two multicenter, randomized, double-blind, vehicle-controlled clinical trials (Trial 1 and Trial 2), 363 adult and pediatric subjects 10 years of age and older with facial acne vulgaris were treated with CABTREO or vehicle topically once daily for 12 weeks Adverse reactions reported by >1% of subjects treated with CABTREO and more frequently than subjects treated with vehicle are summarized in Table 1. These adverse reactions were mild (59%), moderate (36.4%), and severe (4.5%). Overall, 2.5% (6/242) of subjects discontinued CABTREO because of local skin reactions.

Table 1: Adverse Reactions Reported by >1% of Subjects with Facial Acne Vulgaris Treated with CABTREO (and More Frequently than Vehicle) in Trials 1 and 2

Adverse Reactions N (%)		
	CABTREO N=242	**Vehicle N=121**
Application site pain[1]	33 (13.6)	1 (0.8)
Application site erythema[2]	11 (4.5)	0
Application site dryness[3]	10 (4.1)	1 (0.8)
Application site irritation	5 (2.1)	0

Table 1: Adverse Reactions Reported by >1% of Subjects with Facial Acne Vulgaris Treated with CABTREO (and More Frequently than Vehicle) in Trials 1 and 2

Adverse Reactions N (%)		
	CABTREO N=242	**Vehicle N=121**
Application site exfoliation	4 (1.7)	0
Application site dermatitis	3 (1.2)	0

[1]Application site pain also includes application site stinging and burning

[2]Application site erythema also includes erythema

[3]Application site dryness also includes xerosis

Local tolerability evaluations were conducted at each study visit by assessment of erythema, scaling, itching, burning, and stinging. Table 2 presents the signs and symptoms of local facial tolerability at Week 12 in subjects treated with CABTREO.

Table 2: Facial Cutaneous Tolerability Assessment during 12 week treatment period in Subjects with Acne Vulgaris Treated with CABTREO in Trials 1 and 2

	Maximum During Treatment*			**Week 12 (End of Treatment)****		
	Mild n (%)	**Mod n (%)**	**Severe n (%)**	**Mild n (%)**	**Mod n (%)**	**Severe n (%)**
CABTREO (N = 242)						
Erythema	34.2	19.7	2.1	22.4	6.5	0.5
Burning	29.6	10.7	3.0	4.2	1.4	0.9
Scaling	26.7	3.4	0	7.0	0.9	0
Itching	24.3	3.4	0.4	6.0	0.9	0
Stinging	20.5	5.1	2.6	2.3	0.9	0.5
Vehicle (N = 121)						
Erythema	22.5	21.7	1.7	25.5	5.5	0
Burning	2.5	0.8	0.8	0.9	0	0
Scaling	12.5	0	0	4.5	0	0
Itching	11.6	0.8	0	1.8	0	0
Stinging	3.3	0.8	0	1.8	0	0

*The denominators for calculating the percentages were the number of subjects with at least one post-baseline cutaneous tolerability assessment.

**The denominators for calculating the percentages were the number of subjects with Week 12 assessment.

Local tolerability scores for erythema, scaling, itching, burning, and stinging increased during the first two weeks of treatment and decreased thereafter.

BRIEF SUMMARY OF PRESCRIBING INFORMATION This Brief Summary does not include all the information needed to use CABTREO safely and effectively. See full prescribing information for CABTREO.

CABTREO™ (clindamycin phosphate, adapalene and benzoyl peroxide) Topical Gel 1.2%/0.15%/3.1%
Initial U.S. Approval: 2023

DRUG INTERACTIONS

Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use CABTREO with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Available data with CABTREO use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with CABTREO.

Clindamycin
In published clinical trials and observational studies with pregnant women, oral or IV administration of clindamycin has not been associated with an increased frequency of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, clindamycin phosphate did not cause malformations or embryofetal development toxicity in pregnant rats and mice when administered during the period of organogenesis as systemic doses up to 192 times the maximum recommended human dose (MRHD) of 2.5 g CABTREO, based on a body surface area (mg/m2) comparison.

Adapalene
Available data from clinical trials with adapalene topical gel use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of adapalene to pregnant rats and rabbits during organogenesis at dose exposures 64 and 128 times, respectively, the MRHD resulted in fetal skeletal and visceral malformations.

Benzoyl peroxide
The systemic exposure of topical benzoyl peroxide is unknown. Based on published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure of the drug.
The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
Animal reproductive/developmental toxicity studies have not been conducted with CABTREO or benzoyl peroxide. Clindamycin phosphate administration during the period of organogenesis in pregnant rats and mice at oral doses of up to 600 mg/kg/day (192 and 96 times the MRHD), respectively, based on a mg/m2 comparison) or subcutaneous doses of up to 200 mg/kg/day 64 and 32 times the MRHD, respectively, based on a mg/m2 comparison) did not cause fetal malformations or fetotoxicity.
No malformations were observed in rats treated with oral adapalene doses of 0.15 to 5.0 mg/kg/day adapalene (up to 13 times the MRHD based on a mg/m2 comparison). However, malformations were observed in rats and rabbits when treated with oral doses of ≥ 25 mg/kg/day adapalene (64 and 128 times the MRHD, respectively, based on a mg/m2 comparison). Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits. Dermal adapalene embryofetal development studies in rats and rabbits at doses up to 6.0 mg/kg/day adapalene (up to 15 and 30 times the MRHD, respectively, based on a mg/m2 comparison) exhibited no fetotoxicity and only minimal increases in skeletal variations (supernumerary ribs in both species and delayed ossification in rabbits).

Lactation

Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CABTREO and any potential adverse effects on the breastfed child from CABTREO or from the underlying maternal condition.

Clindamycin
There are no data on the presence of clindamycin in human milk, the effects on the breastfed child, or the effects on milk production following topical administration. However, clindamycin has been reported to be present in human milk in small amounts following oral and parenteral administration.

Adapalene
There are no data on the presence of topical adapalene gel or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, adapalene is present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topical administration of large amounts of adapalene could result in sufficient systemic absorption to produce detectable quantities in human milk (see Clinical Considerations).

Benzoyl peroxide
There are no data on the presence of topical benzoyl peroxide in human milk, its effects on the breastfed infant, or its effects on milk production. The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Any amount of benzoyl peroxide excreted into human milk by a nursing mother would be expected to be rapidly metabolized by tissue and stomach esterases.

Clinical Considerations
To minimize potential exposure to the breastfed infant via breastmilk, use CABTREO on the smallest area of skin and for the shortest duration possible while breastfeeding. To avoid direct infant exposure, advise patients who are breastfeeding not to apply CABTREO directly to the nipple and areola. If applied to the patient's chest, care should be taken to avoid infant exposure via direct contact with the infant skin.

Pediatric Use
The safety and effectiveness of CABTREO for the topical treatment of acne vulgaris have been established in pediatric patients 12 years of age and older. Use of CABTREO for this indication is supported by data from two randomized, double-blind, vehicle-controlled trials.

The safety and effectiveness of CABTREO have not been established in pediatric patients younger than 12 years of age.

Geriatric Use
Clinical studies of CABTREO did not include any subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Study of Glabellar Contraction Patterns in African Descendants

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ABSTRACT

Background: Botulinum toxin is a well-established treatment for dynamic glabellar lines. Glabellar contraction patterns were described previously in the general Brazilian population and also among Koreans, Chinese, and Indian individuals. So far, no study has addressed glabellar contraction "patterns" in Black subjects.

Objective: To identify the glabellar contraction patterns in the Black population for a better treatment approach with botulinum toxin treatment.

Method: Pairs of photographs – at rest and under contraction – from 103 Black patients were analyzed according to a previously described classification based on the predominance of eyebrow approximation, depression, or elevation movements. Results: The 5 glabellar contraction patterns described previously – "U," "V," "convergent arrows," "omega," and "inverted omega" – could be identified in these patients.

Conclusion: The classification of glabellar wrinkles enables a more accurate individualized treatment with botulinum toxin in Black subjects, in addition to other ethnic groups.

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INTRODUCTION

The glabella is the first area to be noticed in facial expression, and its contraction is usually associated with negative feelings.[1,2] It is also the most frequently area studied and the first to receive US Food and Drug Administration (FDA) approval for cosmetic botulinum toxin treatment.[3,4]

Contraction of the glabella changes the position and height of the eyebrows, that are fundamental in face recognition and facial expression.[5,6] It involves the action of several muscles such as corrugators and orbicularis oculi (which approximate and depress the eyebrows), procerus and depressor supercili (depressors), and the frontalis muscle (the only lifter of the upper face).[7]

Understanding the importance and necessity of this research lies in recognizing that glabellar expression lines stem from repetitive muscle contractions, which evolve from dynamic lines into static wrinkles over time.[8-10] These wrinkles manifest differently due to various factors such as gender – where men typically exhibit thicker, oilier skin, larger muscle mass, well-defined superciliary arches, a more pronounced glabella,[11] wider facial movements, and more severe facial wrinkles, particularly excluding the perioral area.[12-14] Additionally, factors such as aging contribute, with volume loss and changes in muscle tone or laxity influencing wrinkle formation. Ethnicity, sun exposure, and physical activity further contribute to the variations observed in the development of these wrinkles.[15-17] Understanding these multifaceted influences is crucial for developing effective treatment and prevention strategies.

Although the anatomy is similar among individuals, how individuals engage their musculature varies.[8] A study showed that Europeans have generally larger facial movements than Asians, especially in the eyebrow, nose, and mouth regions. An exception must be made to the eye region, where Asians have a larger excursion of the eyelids.[19] It is important to

understand the aging characteristics, aesthetic concerns, and related problems among diverse populations, and this topic has gained interest in recent years.

Similar to individuals of all ethnic backgrounds, Black people have unique natural features and cosmetic concerns that require a detailed understanding by the treating dermatologist or cosmetic physician.[20-23] The morphology of the skull has some particular features like a shallow and rectangular orbit, a longer forehead, moderate brow ridges, and wide and rounded nasal openings.[11] The skin is thicker, with extra layers of cornified cells, higher melanin content, and a thicker dermis rich with large and active fibroblasts producing collagen bundles that are arranged parallel to the epidermis.[24] These characteristics may protect against sun damage and retard the appearance of aging signs like wrinkles for several years. Conversely, they increase the tendency of melasma and post-inflammatory hyperpigmentation and the risk of the development of keloids after injuries.[24]

Botulinum toxin treatment can improve the severity of glabellar wrinkling in repose and during animation, relax the appearance of the upper face, reduce the frequency of negative facial expressions, and impact the shape and lift of the eyebrows.[25]

Black patients are underrepresented in cosmetic clinical trials, although they form a considerable portion of the global population. In 2020, a systematic review of glabellar botulinum toxin clinical trials in the US found that among 19 randomized controlled trials (RCTs) on BTX-A, only 5.4% of the study participants were Black.[26] Only 3 clinical trials had specifically addressed the glabellar botulinum toxin treatment in Black patients. In those controlled studies, the glabellar wrinkles were considered moderate or severe, and the dose were fixed.[27-29]

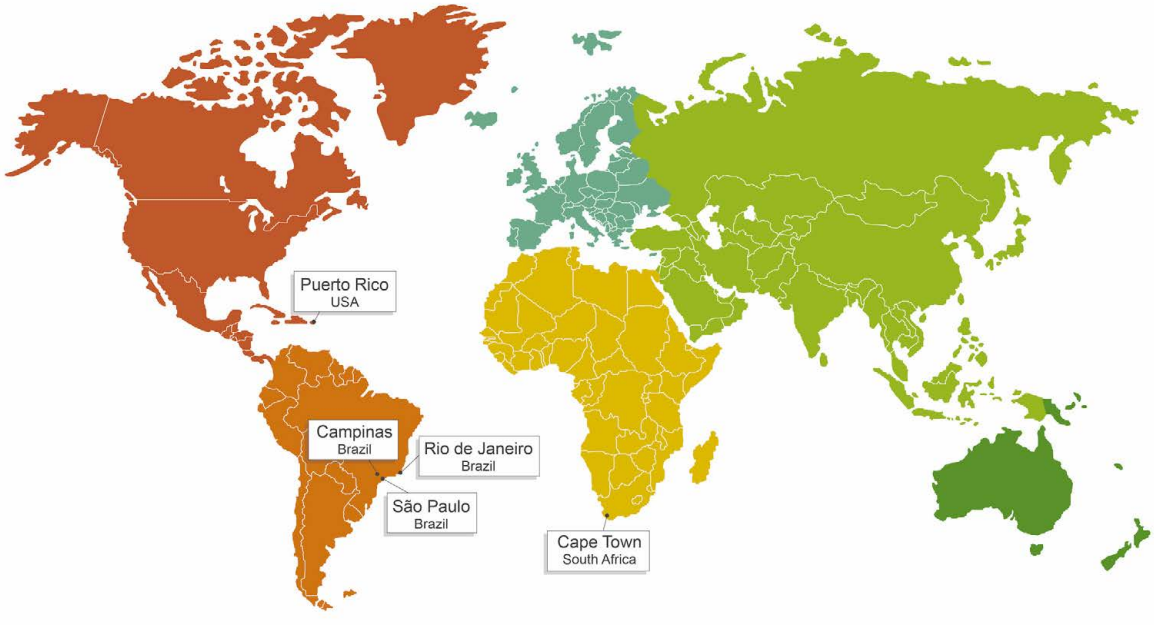
In practice, it is essential to customize treatment based on individual requirements. Understanding the classification of glabellar wrinkles aids in selecting the appropriate dose of neuromodulator aligning it with muscle engagement and mass.[8] Previous studies have outlined glabellar contraction patterns in diverse populations, including Brazilians,[7,18] Koreans,[30] Chinese,[31,32] and Indians.[33]

What makes identifying the glabellar contraction pattern significant? It is crucial for enhancing comprehension of the involved muscles and ultimately devising a more effective treatment strategy with botulinum toxin therapy.[18] So far, no study has addressed glabellar contraction patterns in Black subjects.

MATERIALS AND METHODS

Pairs of photographs – at rest and under contraction – from 103 Black patients were analyzed according to previously described classification based on the predominance of eyebrow approximation, depression, or elevation movements. Patients with a previous history of ablative, surgical, or filler procedures in the region were excluded from the analysis. The photographs were taken at rest and during full contraction of the glabella on the same day using the same camera, lighting, and distance. The subjects' photographs were selected from the authors'

FIGURE 1. Location of the centers that contributed to cases.



private clinics in São Paulo, Campinas, Rio de Janeiro (Brazil), Cape Town (South Africa), and Puerto Rico (USA), and also from the Dermatology Clinic outpatient unit at the Hospital do Servidor Público Municipal of São Paulo, Brazil. These cities are highlighted in their respective countries on the map, as shown in Figure 1.

This study followed the ethical rules of the 2000 Declaration of Helsinki, and all patients consented to be part of the study. For each photograph pair, 2 evaluators (SM and ARTA observed the space between the eyebrows to identify the predominant single or associated movement of approximation (eyebrows come together), depression (lower position than at rest), or elevation (higher location than at rest), and classified these into one of the 5 contraction patterns, named "U", "V", "converging arrows", "omega", and "inverted omega".

RESULTS

A total of 206 photos at rest and under contraction of glabella from 103 individuals were analyzed. Of the cases, 70 (67,96%) were women, and 33 (32,03%) were men, all with Black skin. The patients' ages ranged from 16 to 83 years old (mean 48,73 years). The 5 glabellar contraction patterns described previously – "U," "V," "convergent arrows," "omega," and "inverted omega" – were identified in these patients. Table 1 is a summary of the frequency of contraction patterns according to gender.

"U" Pattern

Seen in 32 (31,06%) Black individuals, this pattern was the most frequently observed in the total group and women (34.28%; Figure 2). In this particular expression, where the space between the eyebrows is narrowed and depressed, there is a varying degree of intensity but limited range observed (the contraction stops before reaching the midpoint of the pupil), creating a movement resembling the letter "U". At rest, the eyebrows maintain an arched position. The muscles involved are the procerus and corrugators. Patients exhibiting this pattern would benefit from treatment using the traditional 5-injection-site model, with the dosage per injection point tailored based on muscle strength.

"V" Pattern

Seen in 30 (29.12%) individuals, this pattern was the second most frequently observed in the total group and men (39.39%).

TABLE 1.

Frequency of Contraction Patterns in Black People According to Gender

Pattern	Male N(%)	Female	Total
U	8 (24,24)	24 (34,28)	32 (31,06)
V	13 (39,39)	17 (24,28)	30 (29,12)
Converging arrows	6 (18,18)	18 (25,71)	24 (23,30)
Inverted omega	4 (12,12)	7 (10)	11 (10,67)
Omega	2 (6,06)	4 (5,71)	6 (5,82)
Total	33 (32,03)	70 (67,96)	103 (100)

FIGURE 2. Clinical photographs showing at left the glabella at static position and at right the "U" pattern of glabellar contraction lines.

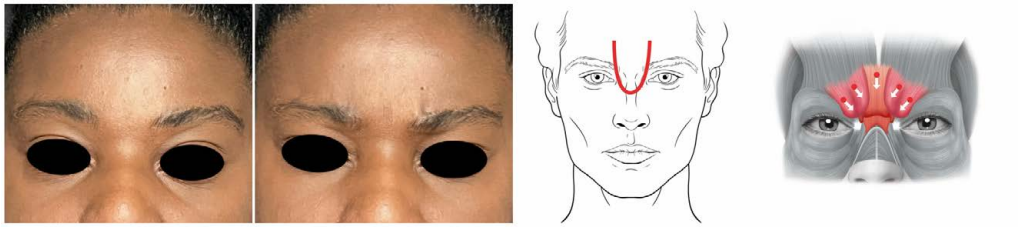


FIGURE 3. Clinical photographs showing at left the glabella at static position and at right the "V" pattern of glabellar contraction lines.

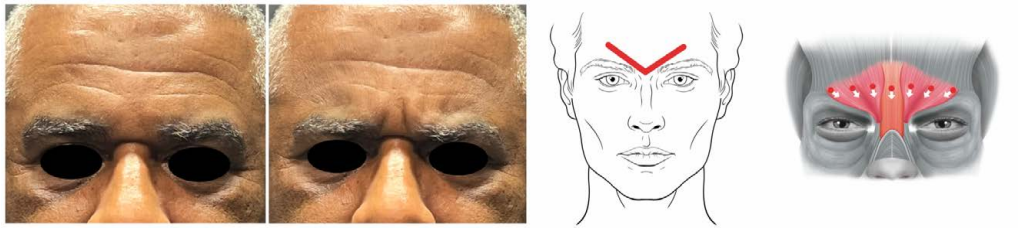


FIGURE 4. Clinical photographs showing at left the glabella at static position and at right the "converging arrows" pattern of glabellar contraction lines.

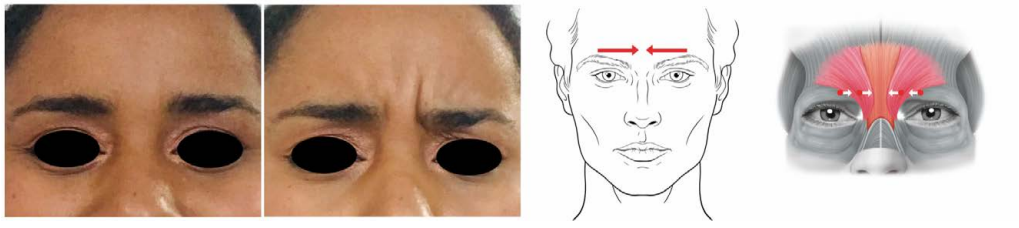


FIGURE 5. Clinical photographs showing at left the glabella at static position and at right the "inverted omega" pattern of glabellar contraction lines.

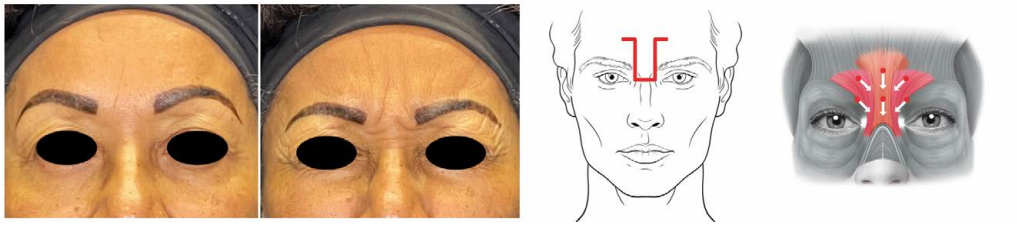
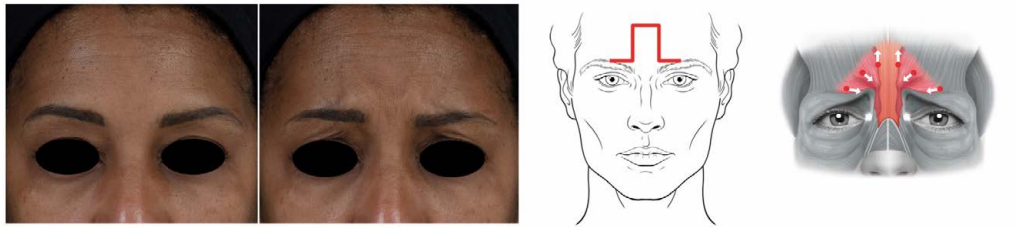


FIGURE 6. Clinical photographs showing at left the glabella at static position and at right the "Omega" pattern of glabellar contraction lines.



(Figure 3). Wide-range approximation and depression of the glabella is observed (the contraction extends beyond the mid-pupillary line). At rest, the eyebrows are flat, rectified, and lower. In addition to the participation of corrugators and procerus, there is also recruitment of the medial portion of the orbicularis oculi muscle. These patients will be better addressed by using the 7-site injection model with doses selected according to the muscle strength but usually concentrated at the procerus and corrugators.

"Converging Arrows" Pattern

Seen in 24 individuals (23.30% of cases), this pattern was the third most frequently observed in the total group, but the second most frequent pattern in women (Figure 4). In this "brow opposers" pattern, the eyebrows mainly get together, with little or no depression or elevation, the final movement being a horizontal approximation. The opposing forces between the procerus and frontalis are balanced. Corrugators and the medial portion of the orbicularis oculi muscles are involved. The injection technique should be more horizontal, targeting the recruited muscles and sparing or using lower doses at those not involved.

"Inverted Omega" Pattern

Seen in 11 cases (10.67%), this pattern was the fourth most frequently observed in the total group, in men, and women (Figure 5). Contrary to the previous pattern, here, the eyebrows barely join each other. The predominant movement is depression far more than approximation. The movement resembles an inverted Omega letter. There is action of depressor supercili, procerus, and the internal portion of orbicularis oculi pars palpebralis muscles, and also recruitment of the nasalis. The most appropriate treatment would be higher doses deposited into the procerus and depressors supercilii and additional sites at the internal portion of the orbicularis oculi pars palpebralis and nasalis muscles. A minimal dose may or may not be injected into the corrugators.

"Omega" Pattern

Seen in 6 cases (5.82%), this pattern was the least frequently observed (Figure 6). In this easy-to-identify pattern, the eyebrows get together and raise at the glabella, taking the form of the Greek letter Omega. There is participation of corrugators, the medial portion of the orbicularis oculi, and co-contraction of the frontalis, but little or no procerus action. The best approach

TABLE 2.

Frequency of Contraction Patterns in General Brazilian Population Compared With Black Population

Pattern	Brazilian Male	Population Female	Total	Black Male	Population Female	Total
U	8 (17,4)	99 (34,4)	107(32)	8 (24,24)	24 (34,28)	32 (31,06)
V	24(52,2)	77 (26,7)	101(30,2)	13 (39,39)	17 (24,28)	30 (29,12)
Converging arrows	9 (19,6)	55(19,1)	64(19,2)	6 (18,18)	18 (25,71)	24 (23,30)
Omega	4(8,7)	30(10,4)	34(10,2)	2 (6,06)	4 (5,71)	6 (5,82)
Inverted omega	1 (2,2)	27(9,4)	28(8,4)	4 (12,12)	7 (10)	11 (10,67)
Total	46(100)	288 (100)	334(100)	33 (32,03)	70 (67,96)	103 (100)

would be injecting toxin into the corrugators, orbicularis oculi, and medial portion of the frontalis muscle, with higher doses into the corrugators and orbicularis and lower doses into the frontalis sites. The procerus would be spared or receive only a minimal dose.

DISCUSSION

In recent years a huge advance in the knowledge of facial anatomy and the aging process has occurred. Regarding upper facial mimetic muscles, anatomical dissection of fresh cadavers detailed the origin and insertion of this musculature and their variations.[34] These muscles originate in the bone or at the superficial fascia, insert into the skin, and are closely associated with each other, with synergistic and antagonist activities.[7] It is the balance between muscles that lift the skin (elevators) and those depressing it (depressors) that control facial expression. Recently dynamic models using body painting techniques have being used to reflect on the surface the action of the underlying involved muscles during facial expressions.[35] This is useful because variations in weight, strength, muscle activity, and muscle insertion sites produce differences in the contraction patterns in different people, and this is what makes each subject unique. Another factor that may impact facial expressions are the languages spoken in the different cultures.[7,36] In the real world, treatment must be tailored to individual needs, and the classification of glabellar wrinkles help us to correctly choose the dose of neuromodulator according to muscle recruitment and mass.

Glabellar contraction patterns were studied previously in the general Brazilian population and also among Korean,[30] Chinese,[31,32] and Indian[33] subjects. They are mainly divided into 2 groups: one based on the predominant movement between the eyebrows and the other based on the wrinkle shape formed between the eyebrows. Our subject sample was predominantly female (63%), with a mean age of 48 years, which is similar to all studies evaluating glabellar patterns of contraction in different populations.

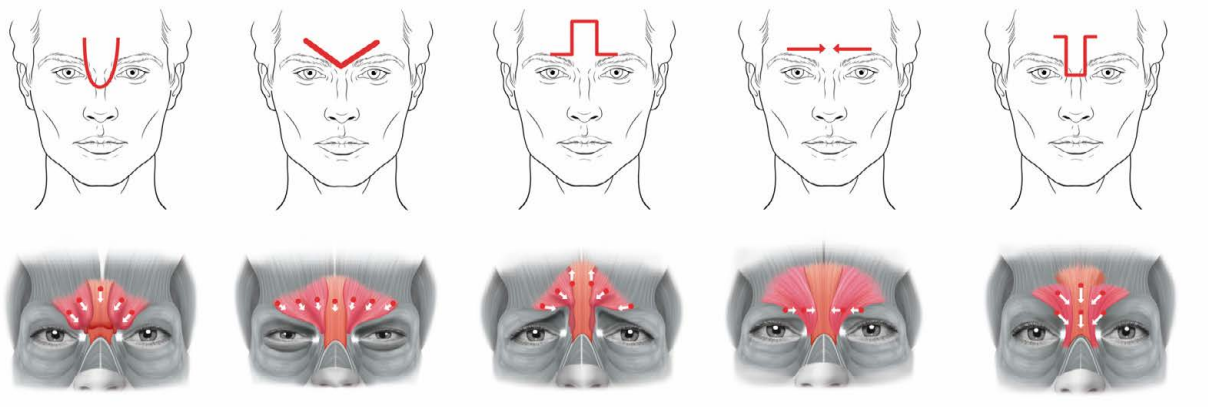
In the general Brazilian population study, the most frequent pattern found was the "U" (also most frequent in females) followed by the "V" type that was more prevalent in men. The distribution pattern was similar to our Black subjects study where the main pattern was "U". In men, the "V" pattern was the most frequently found and in women it was the "U". Table 2 shows the frequency of each contraction pattern found in this study and compared with the De Almeida's trial.

Two retrospective trials with 945 Chinese patients also analyzed the glabellar contractions using the movement-based classification system.[31,32] The most frequent pattern found in that population was the "converging arrows", followed by the "U" type. Their higher frequency of "converging arrows" compared with Westerners was attributed to reduced muscular activity and strength in that population,[30] and also to some anatomical ethnic differences like a flatter nasal apex and shorter corrugators described in a previous study with Chinese cadavers.[37] Black individuals may also have a flat nasal apex and large nose base. Variations in the shape and insertion sites of the corrugator supercili muscle were described in previous publications[34,37]; but we are not aware of cadaveric studies specifically addressing these muscle features in Black subjects. The Black population studied in this sample is made up of the Brazilian population, which is already mixed, and also of Black patients from South Africa and Puerto Rico, unlike other studies in which only one ethnic group was studied.

The Korean and Indian studies used a glabellar classification based on the shape of the wrinkles formed during contraction, and named as "U", "11", "X", "phi(π)" and "I".[30] What is the correlation to De Almeida's Classification? A similar "U" pattern, that was also the most frequent among Koreans, the "11" corresponds to the "converging arrows", their "phi(π)" pattern is the "Omega", their "X" correlates to the "Inverted Omega", while no correlation regarding the "I" type could be done.

The Korean study suggests the natural evolution of the glabellar wrinkles would be initial perpendicular lines (the "11" wrinkles), progressing with the addition of a horizontal line secondary to the procerus involvement (forming the "U" pattern), and posteriorly including the frontalis ("π" and "I" patterns) and/or nasalis muscles ("X" type of wrinkle). In our results this sequence could not be observed, especially in those patients with the "converging arrows-and-omega" patterns of contractions that didn't usually recruit the procerus muscle.

FIGURE 7. Illustration of muscle force vectors and the corresponding glabellar pattern.



In De Almeida's 2012 paper, a subset of patients was analyzed after several botulinum toxin treatment cycles to see if any change in the original contraction pattern occurred after repeated muscle blockage. All patients recovered their initial contraction model when the neuromodulator effect disappeared, recruiting the same muscles as always. This way, the best way to predict the wrinkle formation is to observe the most frequent mimetic muscles recruited for each patient according to their unique features. Figure 7 demonstrates the muscular movement schematically, in each pattern.

The Indian study, in another dark skinned ethnic population, added a new "W" type to the Korean classification, and found the "11" or "converging arrows" to be the most frequent pattern.[33]

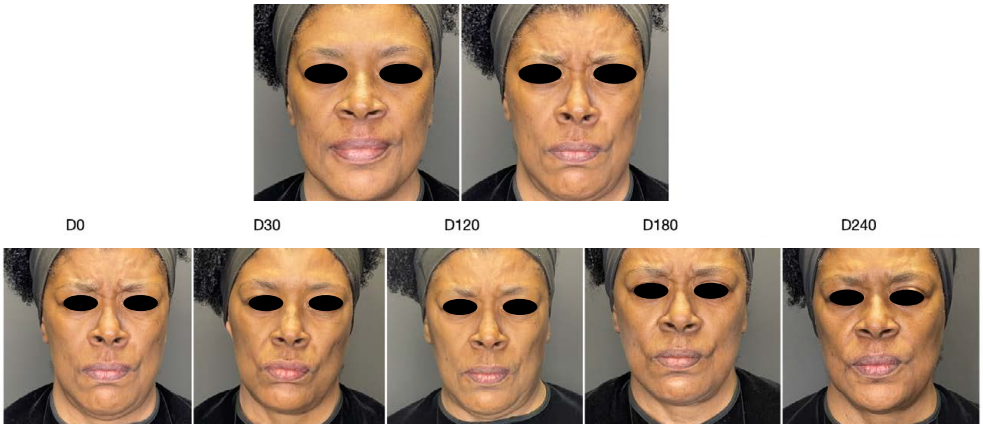
In the second study with Chinese patients, Hsieh et al compared the 2 classification systems[31] and concluded that both classifications could be used on the Chinese population; but since the frequency of certain patterns may be associated with age-related volume loss, De Almeida's classification system provided a more convenient guidance and easy clinical reference for treating Chinese patients in daily clinical practice.

Table 3 demonstrates the most prevalent glabellar contraction pattern in each ethnic group studied so far.

TABLE 3.

Main Glabellar Contraction Patterns in Different Ethnic Groups		
Population	**Main Pattern**	**Percentage**
Black	"U"	31,06%
Korean	"U"	44,6%
Indian	"11" (converging arrows equivalent)	40%
Chinese	Converging arrows	30,3%

FIGURE 8. Top: a 59-year-old Black woman at rest and under contraction, showing a "V" type glabellar pattern. Bottom: Her long-term treatment at day 240.



We know that dynamic glabellar lines, without effective treatment, will become static wrinkles over the time.[8-10] Preventive botulinum toxin treatment has being recommended for maintaining a youthful appearance for a prolonged period in life. Like other ethnic groups, glabellar contraction patterns can also be observed in Black patients. The classification based on the predominant movement can be used in young patients before the formation of wrinkles, but also in older subjects already affected by age-related volume loss. The correct assessment helps the aesthetic physician to adjust the neuromodulator dose and injection sites, to achieve not only an effective initial result but also a long lasting treatment effect. This is demonstrated in Figure 7, which shows a 59-year-old Black woman with a "V" type glabellar contraction pattern and her long-term treatment follow up.

CONCLUSION

The same 5 patterns described previously could be observed in Black subjects, related not to age or gender but to involved muscles. The classification of the glabellar contraction pattern in different ethnic groups leads to individualized, tailored, and improved neuromodulator treatment. It can also be a useful tool to improve botulinum toxin treatments in this population.

DISCLOSURES

Suelen Montagner, Najara Gomes dos Santos, Camila Trindade de Almeida, Izolda Heydenrych, Katleen da Cruz Conceição, and Jose Raul Montes have no conflicts of interest to disclose. Carla de Sanctis Pecora has affiliations with Merz Aesthetics. Cheryl Burgess and Ada Regina Trindade de Almeida have affiliations with Allergan Aesthetics and Merz Aesthetics.

Ethics Statement: This study was approved by the ethics and research committee of Hospital of the Public Servants of São Paulo. (CAAE number: 76911624.8.0000.5442)

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ORIGINAL ARTICLE

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Assessing the Landscape of Artificial Intelligence-Powered Patient Documentation in Dermatology

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ABSTRACT

Background: The prevalence of burnout among United States (US) dermatologists has surged, reaching 49% in 2023, with a growing volume of bureaucratic tasks (eg, charting, paperwork) the leading factor behind professional fatigue. We seek to explore the competitive landscape and efficacy of AI-powered patient documentation to alleviate burnout among dermatologists by optimizing documentation practices while maintaining accuracy.

Methods: We conducted a review of 18 AI-powered automated documentation products available in the current healthcare landscape, focusing on their integration with electronic health record (EHR) systems, HIPAA compliance, language support, mobile accessibility, and consumer type.

Results: The survey revealed AI-powered documentation tools with various features. They aim to reduce clinician burden, enhance workflow, decrease burnout risk, and allow physicians to focus more on patient interaction during visits.

Conclusion: As the technology continues to evolve, AI-powered documentation products have the potential to become an integral part of medicine by enhancing the physician-patient relationship and the overall healthcare system. A thorough evaluation of these products in clinical settings is needed to assess their efficacy. Longitudinal studies should be conducted to determine their impact on physician well-being. Collaboration between stakeholders, including healthcare workers, researchers, developers, and regulatory agencies, is needed to establish guidelines for the integration and use of these products.

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INTRODUCTION

Burnout, a psychological syndrome characterized by emotional exhaustion and a diminished sense of accomplishment in day-to-day work, is a significant concern within the medical community.[1] Recent nationwide survey studies highlight the increasing prevalence of burnout among physicians, including a 2021 study by Shanafelt et al showing 62.8% of physicians reporting at least one symptom of burnout, compared to 45.5% in 2011.[2] The 2024 Medscape Physician Burnout & Depression Report corroborated this finding, reporting that 49% of surveyed US physicians experienced burnout compared to 42% in 2018.[3]

Dermatologists in the United States are no exception, with reported burnout rates reaching 49% in 2023.[4] Leading contributors are bureaucratic tasks (eg, charting, paperwork) and the computerization of practice due to electronic health record (EHR) systems.[4-7] The burden of administrative tasks and the time-consuming nature of documentation processes in dermatology have led to clinician fatigue and compromised the efficiency of healthcare delivery.[8,9]

The impact of burnout among dermatologists extends beyond physician well-being and has negative implications for patient care quality.[9] There is a growing concern regarding the time and attention given to patient interactions and clinical decision-making.[10,11] Thus, there is a need to explore innovative solutions that alleviate burnout while optimizing documentation practices.[8]

In response, significant investments have been made in the healthcare sector, particularly in artificial intelligence (AI). Six billion dollars in 2020 and over $8 billion in 2021 have been invested into the AI healthcare sector to fund the development of AI technologies seeking to improve healthcare delivery.[12] Against this backdrop, recognition of AI-powered solutions and their potential to decrease burnout while enhancing patient care is increasing.

Integration of AI technologies, such as AI-powered patient documentation tools, promises to streamline administrative tasks, reduce clinician burden, and improve efficiency. One solution is AI assistants that use voice recognition, natural language processing (NLP), and artificial intelligence to learn and adjust to a physician's documentation style.[13,14] Using deep learning algorithms; these AI assistants have an advantage over existing voice recognition technologies with advanced natural

language understanding. The goal is to generate notes during patient encounters without the physician needing to manually input them into the EHR. Several AI assistant companies market their products as a less costly alternative to hiring medical scribes.[14]

Despite growing interest and adoption of AI documentation tools, questions remain regarding the accuracy of AI-generated clinical notes and concerns about data privacy and security. This emphasizes the need for a thorough evaluation of these technologies in clinical settings.[15] Our study aims to explore and summarize the current landscape of AI-powered patient documentation within dermatology practice. Through a comprehensive review of existing literature, we seek to provide critical insights into potential benefits and challenges associated with AI-powered documentation.

MATERIALS AND METHODS

A comprehensive review was conducted to identify AI-powered automated clinical documentation products currently available in healthcare. PubMed, Google Scholar, and Scopus were searched using keywords such as "AI-powered documentation," "clinical documentation tools," "dermatology practice," and "physician burnout," Websites of major healthcare technology companies and industry reports were also searched for relevant products.

Inclusion Criteria

Products were included if they met the following criteria: (1) utilized artificial intelligence for automated patient documentation, (2) had relevance to dermatology practice or had potential applicability to dermatology, and (3) had publicly available information regarding relevant features.

Data Extraction and Synthesis

Information about each product was extracted, including: (1) name, (2) launch year, (3) headquarters location, (4) EHR system integration, (5) HIPAA compliance, (6) supported languages, (7) mobile platform availability, (8) primary consumer type, and (9) additional relevant information. Data were synthesized into a review of the landscape of AI-powered automated clinical documentation products. Two independent reviews were performed and verified extraction and synthesis to ensure accuracy and completeness.

RESULTS

Recently, the healthcare industry has seen several companies launch AI-based automated clinical documentation solutions. These products use natural language processing (NLP) and machine learning to extract, organize, and document patient-physician encounters in real time. Companies differentiate themselves based on ease of integration with existing EHRs, skill at differentiating speaker roles, transcription accuracy, documentation types, and extra features like automated coding for billing, patient chart access to augment documentation, multilingual interpretation, and differential diagnoses generation. Below, we introduce several pioneering companies in this field.

Suki AI

Suki offers an AI-powered, voice-enabled digital assistant that uses ambient listening to automate note generation within EHRs. The company's use of NLP minimizes the learning curve for adoption and use. While documentation can proceed without command, verbal dictation and commands are also possible for retrieving key patient information, such as medication lists, allergies, medical histories, and vital signs. The platform also automates ICD-10 codes for encounters and streamlines administrative tasks using EHR patient data.

Dragon Ambient Experience and Dragon Medical One (Nuance/Microsoft)

Nuance, partnering with Microsoft since 2019, offers Dragon Medical One and Dragon Ambient eXperience Copilot (DAX Copilot) AI for clinical documentation. DAX Copilot integrates Nuance's conversational and ambient AI with OpenAI's GPT-4 to generate draft clinical notes after patient visits. Following Epic's announcement of DAX Copilot's general availability in its EHR, over 150 health systems, hospitals, and medical centers are set to adopt the technology. Dragon Medical One, Nuance's other clinical AI technology, facilitates immediate note dictation without voice profile training and can be used independently of or in conjunction with DAX technology.

M*Modal (Owned by 3M)

3M Fluency Direct is a speech and AI-powered solution that allows for creating clinical notes directly within EHRs. It utilizes 3M's natural language understanding and built-in computer-assisted physician documentation (CAPD) for real-time clinical encounter monitoring and analysis. The single cloud-hosted voice profile enables dictation from any device. Additional features like clinical documentation integrity (CDI) and hierarchical condition category (HCC) management enhance accuracy.

Tali AI

Tali AI provides a voice-enabled virtual assistant that incorporates built-in medical scribing and medical search functions. They can be used to dictate notes directly into EHR software, check medication dosages, and access patient charts. Tali AI also offers an ambient scribe feature that automates note generation in real time. All features are accessible on any web-based or desktop EHR following an initial integration process that Tali reports requires minimal installation and training.

Regard AI
Regard AI operationalizes GPT-4 and large language models (LLMs) in healthcare to automate clinical note drafting, offer intelligent autocomplete for documentation editing, and improve accuracy by auditing against clinical guidelines. Regard AI emphasizes its ability to synthesize patient data and recommend diagnoses. Recently, Regard expanded its core product to cover 173 cancer diagnoses, detailing stages, remission, and metastases from patient records. The company also offers a service to identify revenue opportunities.

Deepscribe
DeepScribe integrates AI into clinical documentation through ambient AI, machine learning, and rules-based NLP. It employs a secure iOS application to record real-time patient-doctor interactions, transcribe the data into SOAP notes, and integrate them into existing EHRs. It also uses human quality control for accuracy.

Augmedix
Augmedix offers automated medical documentation and data services through its Ambient Automation Platform. Augmedix Live, its flagship product, employs ambient AI, including NLP and Google's Large Language Model (MedLM), to convert physician-patient interactions into real-time medical notes by securely transmitting patient-clinician interactions to technology-augmented remote medical scribes. It integrates a medical documentation specialist into the care team, offering point-of-care support through two-way messaging. In 2023, the company launched Augmedix Go, an app converting patient visit audio into drafted medical notes.

DeepCura AI
DeepCura offers AI-powered Clinical Automation and Diagnosis Solutions. Leveraging GPT-4 and Bio Clinical Bert, it allows the ability to upload any audio, video, image, or PDF for information extraction and transfer as instructed by the user. Its AI Clinical Containers feature a Prompt Shortcut Library and an AI Clinical Scanner for clinical note generation via prompts or dictation. Notable features include multi-speaker and multilingual transcriptions, customizable SOAP and H&P notes, evidence-based AI Assistant, and a reported industry-record 60-second note turnaround time.

Freed AI
Freed is an AI-driven platform that transcribes patient visits by extracting, summarizing, and organizing information to the users' preferred format. Transcriptions are based on medical guidelines and best practice templates, and notes are reviewable by physicians for editing and transfer into an EHR. Freed utilizes machine learning to mimic the user's writing style and templates. The company emphasizes a commitment to privacy by not storing recordings.

ScribePT
ScribePT's AI listens to patient interactions or recordings and generates preliminary clinical notes. It leverages generative AI to mirror the user's documentation style and then facilitates data transfer to EHR systems. The company reported that new functionalities are being added, including autocompletion, to improve editing and reporting of patient engagement and outcomes. ScribePT also provides automated quality checks for documentation and billing errors.

Ambience
Ambience Healthcare launched a suite of AI products for healthcare: AutoScribe for real-time documentation, AutoCDI for coding, AutoAVS for patient summaries, and AutoRefer for referrals. An AutoPrep functionality for agenda design is also slated to be added. This suite serves in-person, phone, video, and written interactions in English, Spanish, and Mandarin. It employs intelligent speech recognition suitable for various environments, accents, jargon, acronyms, and multi-speaker dialogues. It also uses patient data from EHR inputs to add context to data analytics and note generation.

Mutuo Health
Based in Toronto, Mutuo Health Solutions, established in 2018, introduces the AutoScribe research project to advance medical documentation. Through the project, Mutuo records physician-patient dialogues and employs AI-powered speech recognition and NLP to generate suggested clinical notes and EHR actions in real time.

Scribeberry
Scribeberry offers a platform for converting spoken or typed input into medical notes and generating SOAP notes, letters, and forms using customizable templates designed for easy editing, copying, and pasting into existing EHRs. The technology supports transcription from recorded audio and offers relevant summaries derived from information extracted from the audio recordings. The company cites up to a 60-70% reduction in charting time.

Speke (Scribe America)
Speke, offered by Scribe America, is an ambient AI scribe that converts natural conversations into accurate notes using speech-to-text and NLP. Providers need only to review and sign off within the EHR once documentation is complete. Speke is advertised as adaptable across different care settings and sub-specialties, with a concierge team assisting in the integration of it according to individual workflow preferences. ScribeAmerica medical scribes oversee documentation for accuracy and quality.

Nabla
Nabla Copilot, a French startup launched in March 2023, leverages a combination of Microsoft's speech-to-text API, a

Whisper model, and GPT LLMs to generate concise clinical notes. Notably, Nabla ensures the privacy of personally identifiable information (PII) by masking it during processing and only unmasking it post-output. Nabla prioritizes data security by not storing the speech or the summarized notes without explicit physician and patient consent. According to Nabla, only 5% of generated notes require adjustments.

Abridge

Founded in 2018, Abridge is an ambient AI company that converts patient-clinician conversations into structured clinical note drafts in real time. The AI system encompasses decision-making insights and provenance tracking for accountability. In addition to note generation, the platform is able to aid in telehealth experiences, care coordination, and supporting population health programs.

Innovaccer Inscribe

Innovaccer InScribe, launched Sara Scribe, an AI-powered healthcare documentation tool for transcribing and analyzing patient-clinician conversations in real-time. It offers SOAP visit summaries, assessment suggestions, and linking of relevant portions of notes back to the transcription. InScribe caters to enterprise integration with Innovaccer's InNote and independent practitioners through a standalone web-based tool. InScribe also leverages AI for clinical insights on care quality and potential diagnoses. The platform lists differential diagnoses as an upcoming feature on its website. InScribe claims 90-95% transcription accuracy and SOAP note drafting accuracy.

AWS HealthScribe

AWS HealthScribe, powered by Amazon Bedrock, is a HIPAA-eligible service for healthcare software vendors seeking to integrate speech recognition and generative AI into clinical applications. It utilizes a single API to identify speaker roles, classify dialogues, extract medical terms, and generate preliminary clinical transcripts and notes. The technology further provides traceable transcript references for every AI-generated summary. It is utilized by various customers and partners, including 3M M*Modal, Netsmart, Suki, ScribeEMR, Teletracking, and Pariveda.

DISCUSSION

This paper carries out a comprehensive survey of products that use AI-based clinical documentation solutions in the current landscape of artificial intelligence use in medicine. Eighteen products were reviewed for HIPAA compliance, EHR system integration, language options, mobile platform availability, and primary consumer type. These AI-powered tools aim to reduce clinician burden, enhance workflow efficiency, and potentially mitigate burnout risk.

AI-powered documentation can significantly improve the quality of patient visits. By automating routine documentation, these tools free up physicians to focus more on patient interaction, potentially leading to more thorough, personalized care. For solo practitioners or residents who often see patients without scribes, these products can serve as an assistant. This support aids in reducing the stress on these providers and enhances the quality of patient care. Consequently, AI-powered documentation tools represent an advancement in effective healthcare delivery.

The adoption of AI-powered documentation tools also raises challenges and considerations. A primary concern is the accuracy and reliability of AI-generated clinical notes. While the natural language processing capabilities can be easily demonstrated, questions remain regarding the consistency and validity of the capturing, contextualizing, and documenting of AI-processed information. Many reports about artificial hallucinations have been made where AI-powered products present false information as a fact.[16] This includes OpenAI, a software that is currently being used in several AI-powered encounter documentation products. Furthermore, the adoption of these products might not result in an overall reduced clinical burden on physicians. If an AI-generated note is not congruent with the physician's established framework for completing notes, it might increase the burden due to the discrepancy and the effort required to edit the generated note.

Our review highlights the importance of thorough evaluation and validation of AI-powered documentation tools in clinical settings. While these technologies have the potential for addressing burnout and enhancing documentation, their efficacy and safety must be assessed through longitudinal studies. There needs to be collaboration between stakeholders, including healthcare workers, researchers, developers, and regulation agencies, to establish guidelines for responsible integration and use of AI-powered documentation tools. In the future, continued investment in AI research and development, along with interdisciplinary collaboration, will be essential in creating AI solutions to improve dermatology practice and healthcare.

CONCLUSION

AI-powered documentation products present a potential solution to burnout in dermatology by offsetting the demands of bureaucratic tasks. However, successful implementation of these products requires consideration of their limitations. As the technology evolves and stakeholders address these concerns, we will likely see increased adoption of the products across healthcare, leading to changes in healthcare delivery. The potential of the products suggests that AI-powered tools will become an integral part of medicine in the future, enhancing the physician-patient relationship and improving the overall system.

TABLE 1.

Companies Offering AI-Powered Automation of Clinical Encounter Documentation

Company/ Product	Year Launched	Headquarters	Established EHR Integrations	HIPAA Compliant	Languages Offered	Mobile Offering	Primary Consumer Type
Suki AI	2017	Redwood City, CA	Epic, Cerner, Athena, Meditech, Elation	Yes	Not specified	Yes	Private practice
Dragon Ambient Experience and Dragon Medical One (Nuance and Microsoft)	2020 (DAX), Medical One 2018 (Mobile One)	Burlington, MA	Compatible with most EHRs through a cloud-based platform Specific use advertised with Epic, Oracle, Allscripts, MediTech and corresponding mobile HER (Epic Haiku and Canto Cerner, PowerChart Touch, MediTech Expanse)	Yes (specified for Medical One)	Not specified	Yes	Hospitals/inpatient and outpatient clinics
M*Modal (Owned by 3M)	2013	Franklin, TN	> 250 EHRs, including Epic, Cerner, athenahealth, MEDITECH, Altera Digital Health, eClinicalWorks, Greenway Health, NextGen	Yes	Not specified	Yes	Hospital/Inpatient
Tali AI	2020	Toronto, Canada	OscarPro, June; infrastructure can be adapted to remaining EHR	Yes	English, French and Spanish	Yes	Outpatient health clinics
Regard AI	2020	Los Angeles, CA	Epic and Cerner	Yes	Not specified	n/a	Hospitals and small/ private provider groups
Deepscribe	2017	San Francisco, CA	Athenahealth, practice fusion, ElationHealth, Dr. Chrono, NextGen, Tebra, AdvancedMD, ClaimpowerX	Yes	General American English	Yes	Private Practice/ small provider groups
Augmedix	2012 (Live), 2023 (Go)	San Francisco, CA	50+ EHR systems	Yes	Not specified	Yes	Medical clinics, hospitals, emergency department, urgent care clinics, home visits, telemedicine
DeepCura AI	2022	San Francisco, CA	Epic and Dr. Chrono; 5 more integrations in progress	Yes	Not specified; Translation to various languages available	Yea	Individual and small group providers
Freed AI	2022	Santa Rosa, United States	No specific integrations	Yes	Not specified	Yes	Individual and small group providers
ScribePT	2023	Greenwich, CT	Integration/upload to EHR required	Yes	Not specified	Yes	Small Group providers
Ambience	2023	San Francisco, CA	Epic, Cerner, Athenahealth, eClinicalWorks, Elation, AdvancedMD	Yes	English, Spanish, Mandarin, Others	Yes	hospitals /inpatient
AutoScribe (Mutuo Health)	2023	Toronto, Ontario, Canada	PS Suite, Oscar EMR, Cerner, Epic; More integrations in progress	Yes	English and French	Yes	Individual and small group providers
Scribeberry	2023	Toronto, Canada	No direct EHR integration	Yes	Not specified	Yes	Private practice, small clinics to hospitals
Speke, Scribe America	2019	Fort Lauderdale, FL	Established integrations with >100 EHRs	Yes	Not specified	Yes	Outpatient
Nabla Copilot	2023	Paris, France	NextGen, OPUS, AryaHealth	Yes	English, French, Spanish; plans for mandarin, Russian and Arabic 2024	Yes	Outpatient/Private Practice
Abridge	2018	Pittsburgh, PA	EPIC, Priority Health, University of Kansas, Emory and UPMC partnerships	Yes	Not specified	Yes	Hospitals
Sara Scribe (Innovaccer Inscribe)	2024 (announced 2023)	San Francisco, CA	Most major EHR's per statement at JPM24; none specified	Yes	English	Yes	Independent practitioners and small provider groups
AWS HealthScribe	2023	Seattle, WA (Amazon)	Requires developers to add medical speech-to-text capabilities to their applications using APIs	Yes	English	No	Healthcare software vendors

EHR, electronic health record

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

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Expert Recommendations on the Use of a New Hyaluronic Acid Injectable for the Aesthetic Treatment of the Chin and Lower Face

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ABSTRACT

The Restylane® portfolio of hyaluronic acid (HA) fillers comprises a broad range of products, each with a unique combination of gel strength/firmness and flexibility. Restylane® Shaype™ (HA_{SHA}) is a new HA injectable produced with NASHA-HD™ technology and the most recent addition to the Restylane portfolio. NASHA-HD is an evolution of the NASHA™ platform that adds more HA and uses a more efficient cross-linking even though the degree of modification is kept low. HA_{SHA} has an HA-concentration of 25 mg/mL and a G prime (G′) of 916 Pa (0.1 Hz). Experts recommend using HA_{SHA} for treatment in the chin area because its high G′ allows a higher degree of correction/projection with lower injection volumes, especially in those patients with pronounced chin retrusion, together with a long duration of effect and good overall safety. Depending on the patient's needs and the aim of treatment, different approaches and injection techniques should be applied. This paper reflects the recommendations of an interdisciplinary expert panel for the use of HA_{SHA} for the correction of the chin area, including patient selection, product volume, product placement, injection technique, and post-treatment care. Recommendations were discussed and agreed as a consensus, according to cross-sectional expertise and clinical experience.

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INTRODUCTION

The Restylane® portfolio of hyaluronic acid (HA) fillers is engineered by 2 different and complementary technologies; NASHA™ and OBT™/XpresHAn™. Together, these 2 technologies allow for a broad range of products, each with a unique combination of gel strength/firmness and flexibility. NASHA gels (Restylane® and Restylane® Lyft™; Galderma, Uppsala, Sweden) are generally firm with high G prime (G′), while OBT gels (Restylane® Defyne™, Refyne™, Kysse™, and Volyme™; Galderma, Uppsala, Sweden) are softer and flexible, as demonstrated by their high xStrain.[1]

Restylane® Shaype™ (HA_{SHA}; Galderma) is a new HA injectable produced with NASHA-HD™ technology, and the latest addition to the Restylane portfolio. NASHA-HD is an evolution of the NASHA platform that incorporates more HA and employs a more efficient cross-linking while maintaining the same low degree of modification. This results in the product being even firmer compared with all other NASHA gels. HA_{SHA} has an HA-concentration of 25 mg/mL and G′ of 916 Pa (0.1 Hz) and was specifically developed for lower face shaping and to be injected deeply on bone.[2] In 2023, the product was first approved in Canada for temporary augmentation in the chin region.

While numerous clinical papers on the performance and safety of HA-fillers have been published in peer-reviewed literature, clinical guidance on the safe and optimized treatment approach for specific products or anatomical locations in real-world practice is more limited. An international consensus regarding the use of gel science to differentiate the choice of HA fillers for anatomical regions of the face was recently published.[3] Additionally, expert recommendations on the use of an HA filler (Restylane® Eyelight™; Galderma, Uppsala, Sweden) for tear trough rejuvenation were published in 2022.[4]

This paper aims to provide clinical guidance for the safe and optimal use of HA_{SHA} in the chin area, as well as identifying other potential facial areas where the product may be used. Clinical guidance is based on recommendations provided by dermatologists and plastic surgeons with clinical experience injecting HA_{SHA} in a real-world patient population.

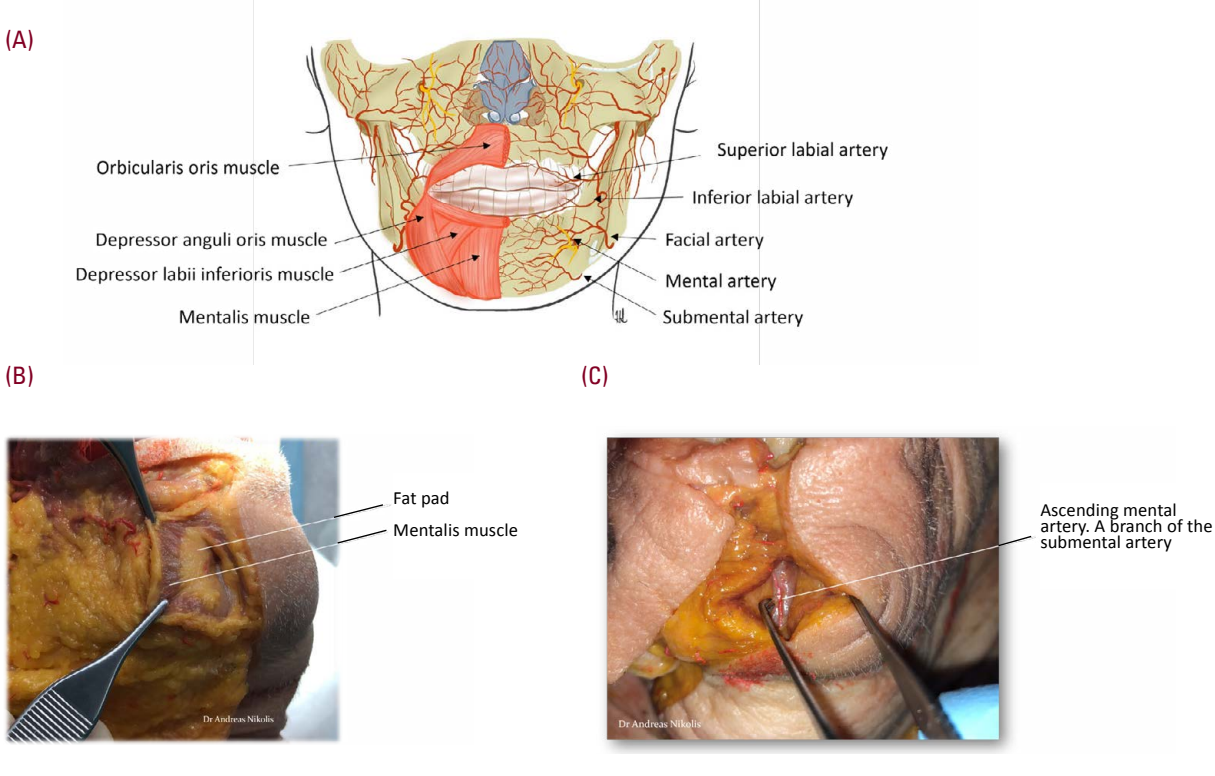
Essential Aspects of Chin Anatomy

Key surface landmarks used to describe the chin are the pogonion – the most anteriorly projecting point on the chin; the menton – the most inferiorly projecting point; and the gnathion – the midpoint between the pogonion and menton.[5]

The chin area has a rich vascular network with interconnected arteries that vary in pattern and location between individuals. The mental arteries, which provide the primary blood supply to the chin, are terminal branches of the inferior alveolar arteries that arise from the maxillary artery. The inferior labial artery and labiomental artery also provide blood supply to the area. The submental artery is the largest of the cervical branches of the facial artery; it arises as the facial artery exits the submandibular gland and gives rise to the vertical labiomental artery. An illustration of muscles and key blood vessels of the lower face is shown in Figure 1A, while photographic images of the mentalis muscle and the ascending mental artery are shown in Figures 1B and 1C. The mentalis muscle provides major vertical support for the lower lip. It is a cone-shaped muscle with its apex originating from the incisive fossa of the mandible, and its medial fibers descend anteromedially and cross each other, forming a dome-shaped pattern. Contraction of the mentalis muscle forms the skin dimples of the mentum, and resection may cause the patient to drool and may affect the denture stability.

Sensory innervation to the chin and lower lip is provided by the mental nerve, which arises as the inferior alveolar nerve exits the mandible through the mental foramen.[6]

FIGURE 1. Illustration of (A) muscles and key blood vessels of the lower face, and images of (B) the mentalis muscle and (C) ascending mental artery. Illustration (A) courtesy of Dr Hani Sinno. Images (B) and (C) courtesy of Dr Andreas Nikolis.



METHODOLOGY

Nine experts (plastic surgeons and dermatologists) from Canada, with extensive clinical experience in aesthetic medicine and experience in the use of HA_{SHA} both as clinical investigators and in the clinic setting, convened in March 2024 to discuss the optimal use of HA_{SHA} for treatment in the chin area, with the aim to simplify and align clinical guidance. Agreement of all experts on the recommendations for the use of HA_{SHA} for treatment in the chin area constituted consensus; subsequently, this formed the basis of the recommendations provided here.

RECOMMENDATIONS

Treatment Aim

The experts agreed that optimal results depend on a variety of factors, including the patient's baseline anatomy, aesthetic preferences (including gender and ethnic considerations), degree of correction required, and expectations of treatment outcome. In general, following facial assessment, treatment aims should include a correction of bone support, an improvement in the projection and/or elongation of chin appearance (in proportion to the face overall), and contouring.

Patient Expectations

Chin projection, shape, and its impact on the facial profile are important components of facial attractiveness in all patients. There can also be improvements in the appearance of the jawline and submental fullness when chin proportions are optimized. Chin retrusion may be perceived as less attractive and associated with a desire for chin correction or elongation.[7,8]

In a prospective, randomized, controlled, evaluator-blinded clinical investigation, subjects treated with HA_{SHA} were satisfied or very satisfied with the shape of their chin at months 3 and 12 following injection (month 3: 93% of subjects; month 12: 87% of subjects), the projection of their chin (month 3: 94%; month 12: 87%), and their chin profile (month 3: 93%; month 12: 82%).[2] In addition, at months 3 and 12 post-injection the subjects agreed or strongly agreed that their chin looked natural (month 3: 95%; month 12: 95%) and that treatment made them feel more attractive (month 3: 71%; month 12: 72%), improved their overall satisfaction with their appearance (month 3: 92%; month 12: 81%), and made them feel better about themselves (month 3: 79%; month 12: 77%).[2]

HA_{SHA} is a non-permanent HA injectable, and hence, the effect is expected to gradually diminish with time. In a prospective clinical trial, the blinded evaluator responder rate measured using the Galderma Chin Retrusion Scale (GCRS) (responders defined as ≥ 1-point improvement from baseline on the GCRS) was 83%, 80%, and 66% at 3-, 6- and 12-months post-injection, respectively.[2]

Clinical experience indicates that the majority of patients seeking treatment to improve the look of the chin describe the desired results in terms of wanting natural-looking improvements in their chin shape, projection, and profile so that they feel better about their overall appearance. Patients may describe themselves as having a 'weak chin' or noting a longstanding lack of definition to their lower face; they may be unable to articulate that their chin is the area requiring treatment but note a desire for improved facial balance/proportions. When seeking improvements, it is critical that the patient is governed by realistic expectations and not by idealized images obtained through social media channels.

Patient Selection

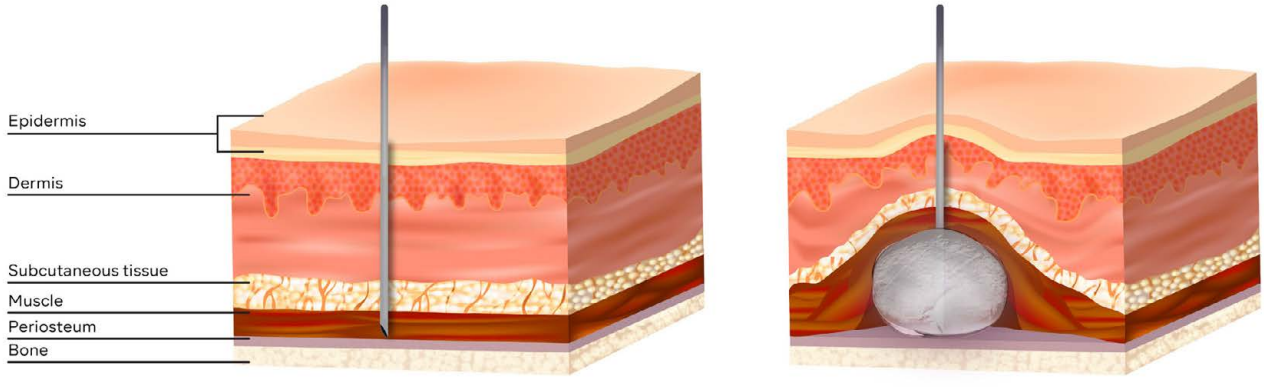
Patients may include males and females who desire augmentation, reshaping, or correction of a chin retrusion and require a non-surgical option with rapid recovery.[2]

The Nikolis et al study[2] was designed to select specific patients based on key inclusion and exclusion criteria and to use specific endpoints to minimize bias when measuring the treatment effect. The primary endpoint was level of improvement of chin projection, and the duration of this effect was measured as the patient responder rate using the GCRS. However, the real-world patient population is more heterogenous compared with a study population, with greater variability in patient and treatment requirements. In addition, in real clinical practice, the treatment protocol may be more optimized to meet the variable patient needs. The expert panel suggested that assessment of the patient's chin projection, shape, and length should be performed in proportion to other structures (such as lips, bigonial width, jawline contour, and nasal and cheek projection). This must also be done in the context of the patient's aesthetic preferences, as well as gender and ethnic considerations. Assessment should ensure that the patient understands the nature of the treatment and has realistic goals and expectations of treatment outcome.[9,10] The expert panel also indicated the importance of assessing the area for prior treatment (such as previous implants or injectables), enquiring about recent dental procedures, and counselling the patient regarding expected temporary pain, swelling, and discomfort.

Use of Product

The expert panel considers HA_{SHA} a good choice for augmentation of the chin area because of its high strength/firmness (high G'). The product is to be injected deeply on the periosteum, and hence a firm product with the ability to resist compression caused by overlying tissues and mentalis muscle contraction is required (Figure 2). Despite its firmness, HA_{SHA} can be molded and shaped to achieve the desired effect.

FIGURE 2. Illustration of injection of HA_{SHA} at the supraperiosteal plane and subsequent lifting of the superior layers of the skin.



Treatment Protocol

Prior to Injection

Injectors should adhere to standard aseptic techniques to help prevent cross-infection. This includes the use of medical gloves and thorough cleaning of the patient's face with a suitable antiseptic solution that extends into the area of and adjacent to the chin. Make-up in the treatment area should be removed. Patients should provide informed consent that includes taking photographs at rest and with animation (smiling) from frontal, 45-degree, and profile views.

Patient assessment is an important step prior to injection, and the Galderma Facial Assessment Scale may be used for this purpose.[11] Patients should have an active role in treatment planning and provide input on desired outcomes.

Some patients may choose to use additional pain relief following the procedure.

Aim of Treatment and Injection Approach

Prior to injection, some injectors prepare by marking the midline of the chin, as well as the horizontal thirds. For males, it is also helpful to mark the vertical medial canthal lines (Figure 3). The most frequent procedures focus on rounding the chin (for a traditionally feminine appearance), squaring/widening the chin (for a traditionally masculine appearance), and contouring the chin to improve the projection of a receded chin or elongate the chin to balance the middle and lower thirds of the face, or a combination of the above. Different approaches were identified that vary depending on whether the aim of treatment is to achieve projection, elongation, or a combination of both, and if the purpose is to achieve a traditionally feminine or traditionally masculine appearance. The different approaches are: chin projection to improve the anterior projection of the chin to create a traditionally masculine appearance with a possible wide and squared base; chin projection to improve the anterior projection of the chin and the look of a receded chin to create a traditionally rounded feminine appearance; chin elongation to increase the perceived length of the chin to balance the facial lower third with the midface for a traditionally masculine appearance; chin elongation to increase the perceived length of the chin to balance the facial lower third with the midface for a traditionally feminine appearance; and chin projection and elongation to improve anterior projection and perceived length of the chin to balance the middle and lower thirds of the chin for a traditionally feminine appearance (Table 1). Injection guidance is provided in Table 1 and Figure 4.

FIGURE 3. For a traditionally masculine appearance, divide the face into vertical fifths and mark vertical internal intercanthal lines if using a wide approach.

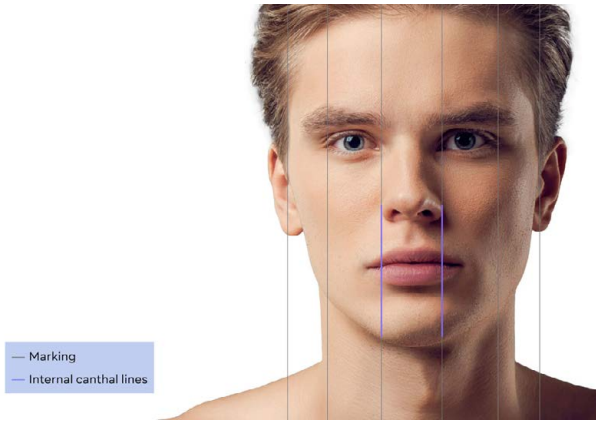
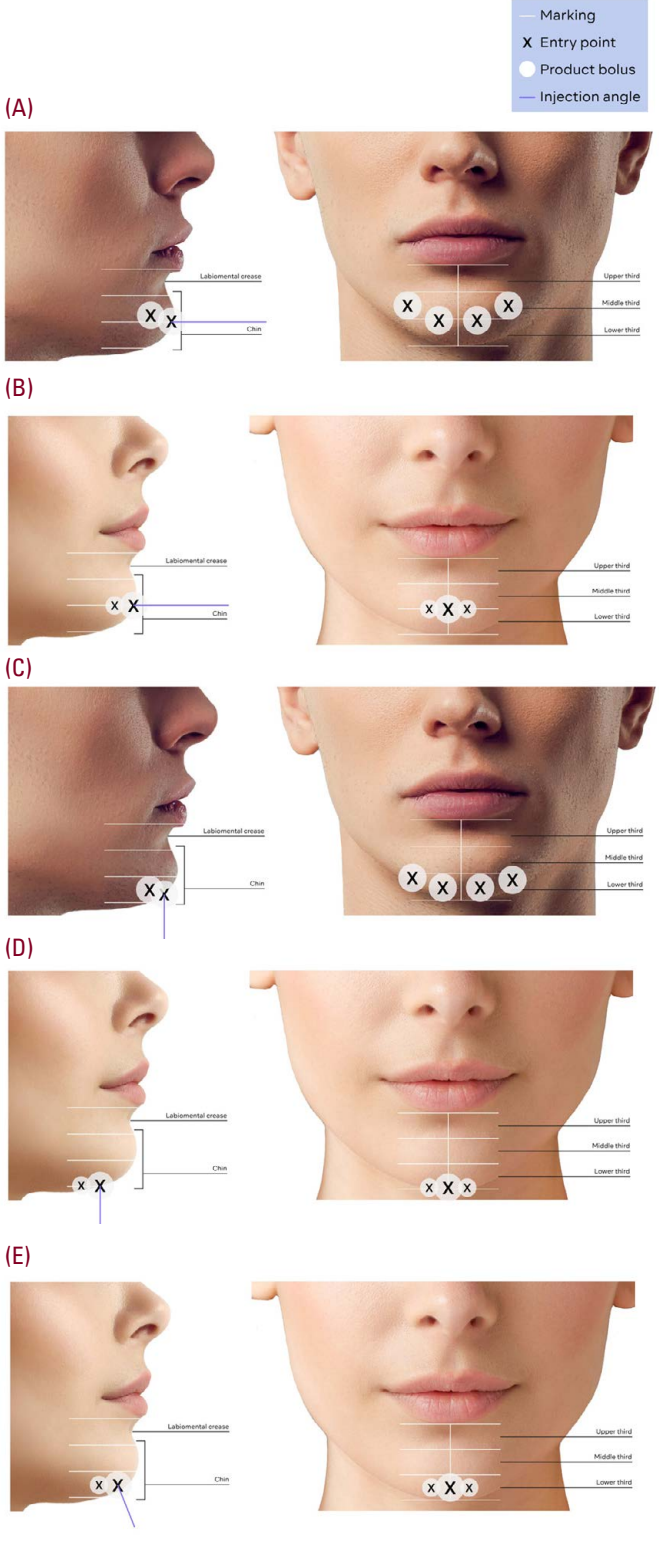


TABLE 1.

Injection Guidance for Chin Projection and Elongation With HA_{SHA}

Approach	Injection Point(s)	Entry Point Location	Procedure	Volume	Technique	Sessions	Injection Delivery	Plane	Alerts
Chin projection Wide, square, traditionally masculine appearance	4	Both sides of the midline within *mid to lower third* of the mandible. A wide approach situates the lateral points at the internal canthal lines.	Insert needle perpendicular to the skin until it touches the periosteum. Aspirate. Slowly inject to the *anterior part of the pogonion*. Massage and mold the area to the ideal shape	1-2 mL per session	Bolus	1-2	Co-packed needle (27 G)	Supra-periosteal	Vascular structures in area
Chin projection Rounded, traditionally feminine appearance	1-3	Midline of the chin. A single injection point may be used, unless the patient has a wider chin and requires 2 injection points, one on each side of midline.		1-2 mL per session (wider chin: 0.5-1 mL central bolus /0.25-0.5 mL side boluses)	Bolus	1-2	Co-packed needle (27 G)	Supra-periosteal	Vascular structures in area
Chin elongation Traditionally masculine appearance	4	Both sides of the midline within *lower third* of the mandible, along the border. A wide approach situates the lateral points at the internal canthal lines.	Insert needle perpendicular to the skin until it touches the periosteum. Aspirate. Slowly inject into the *inferior border of the mandible*. Massage and mold the area to the ideal shape	1-2 mL per session	Bolus	1-2	Co-packed needle (27 G)	Supra-periosteal	Vascular structures in area
Chin elongation Traditionally feminine appearance	1	Midline within lower third of the mandible, along the border. A single injection point may be used, unless the patient has a wider chin and requires 2 injection points, one on each side of midline.		1-2 mL per session	Bolus	1-2	Co-packed needle (27 G)	Supra-periosteal	Vascular structures in area
Chin projection and elongation Traditionally feminine appearance	1-2	Midline of the chin within lower third of the mandible. Sometimes a 1-point technique is not enough to create chin projection and elongation in moderate to severe cases, a duo approach is recommended.	Insert needle perpendicular to the skin until it touches the periosteum. Aspirate. Slowly inject into the *lower third of the mandible*. Massage and mold the area to the ideal shape	2 mL per session	Bolus	1-2	Co-packed needle (27 G)	Supra-periosteal	Vascular structures in area

FIGURE 4. HA_{SHA} injection technique and entry points for: (A) Chin projection, traditionally masculine appearance. (B) Chin projection, traditionally feminine appearance. (C) Chin elongation, traditionally masculine appearance. (D) Chin elongation, traditionally feminine appearance. (E) Chin projection and elongation, traditionally feminine appearance.



The chin area has a rich vascular network (Figure 1A), and it is critical that the injector has adequate knowledge about the anatomy at and around the site of injection to minimize the risk of intravascular injection or compression of vessels, nerves, or other vulnerable structures. Vascular occlusion may cause infarction, necrosis, blindness, or stroke.

Stepwise approaches explaining how to dissolve an incorrectly placed HA implant using hyaluronidase are described in detail elsewhere.[12-15] In addition, clinicians are encouraged to have arrangements in place with a local ophthalmologist in the event of an intravascular ophthalmic adverse event.

Product Volume

The preferred maximum volume of HA_{SHA} is 1 mL to 2 mL at first treatment and up to an additional 1 mL to 2 mL if touch-up is needed. Initially, use of conservative volumes and under-treatment rather than over-treatment is recommended. A separate touch-up treatment will help to achieve optimal results. Product volume requirements will differ from patient to patient and adjustments should be made based on anatomy (eg, a small vs a large chin) and the level of correction desired.

In the Nikolis et al study, post-hoc subgroup analyses showed a possibly clinically significant relationship between total injected volume (initial plus touch-up) and product-related adverse events: 22.4% of subjects injected with a median volume of > 2.8 mL reported a product related adverse event (including pain) compared with 13.2% of subjects injected with a median volume of ≤2.8 mL.[2]

Experts suggest that pain may be minimized by using the smaller volumes noted above and taking a staged approach over multiple sessions to achieve optimal outcomes. The occurrence of pain has been suggested to be caused by product placement deep on the bone in the space under the mentalis muscle, hence causing pain during facial movements due to contractions of the mentalis muscle. Clinically, the initial injection endpoint may be a stiff mentalis muscle on palpation demonstrating appropriate fullness of the region. Counselling patients on the potential occurrence of pain prior to treatment is helpful to prepare them for the procedure and manage expectations. Swelling may also be more pronounced with larger injection volumes. Lastly, more superficial injection of HA_{SHA} can produce contour irregularity and is not advised.

Product Placement

The experts recommend injection of HA_{SHA} on the periosteum below the deep mental fat pad and the mentalis muscle. Caution must be taken to avoid accidental injection into or compression of the submental artery. Localized superficial ischemia and necrosis with potential scarring may occur after injection in or near blood vessels. Intramuscular injection should be avoided as this may result in hematoma and pain.

FIGURE 5. Case 1: before and after treatment with HA_{SHA}.

1 mL HA_{SHA} injected into the chin. 0.5 mL HA_{LYFT} injected per side into the pyriform fossa. 1 mL HA_{LYFT} injected per side into the lateral cheek area. 1 mL HA_{LYFT} injected per side into the jawline. 0.5 mL HA_{DEF} injected per side for transitions. *Pictures courtesy of Dr Andrei Metelitsa.*

FIGURE 6. Case 2: before and after treatment with HA_{SHA}.

1 mL HA_{SHA} injected into the chin with 3 injection points. *Pictures courtesy of Dr Katie Beleznay.*

Injection Technique

The recommended needles for HA_{SHA} injection are provided (co-packed) in the carton with the syringe. The package contains disposable sterile TSK 27G Ultra-Thin-Wall x ¾" (19 mm) injection needles. The experts suggest it is also acceptable to inject HA_{SHA} using a cannula, but placement on bone using a cannula is considered an advanced technique for experienced injectors.

The experts advise using a bolus technique with 1 to 4 injection points depending on the approach and facial anatomy. For projection, locate 1 injection point centrally on the midline of the chin, or 2 injection points on each side of the midline if a slightly wider point of projection is preferred. For elongation, locate 1 injection point centrally on the midline within the lower third of the mandible along the border, or 2 injection points on each side of the midline within the lower third of the mandible, along the border (Table 1 and Figure 4).

As vascular occlusion may cause infarction, necrosis, blindness, or stroke, experts recommend aspirating and holding for >5 seconds and, if there is no sign of blood, proceeding with injecting while recognizing that a negative aspiration does not guarantee avoiding intravascular needle placement.

Case studies involving 2 females illustrate the visual impact of treatment with HA_{SHA} in the chin region (Figures 5 and 6).

Post-Injection Care

Post-treatment care is similar to that required with other HA fillers and patients should receive routine standard of care from their practitioner. If the treated area is swollen directly after injection, an ice pack with adequate protective cloth may be applied to the site for a short period. Gauze or other materials can also be used to protect the skin from direct thermal injury. Use ice with caution if the area is still numb from anesthetic to avoid thermal injury.

Other Areas for HA_{SHA} Injection in Real-World Settings

Experts identified the jawline as an additional area that might be treated with HA_{SHA}. The following is a brief description of the suggested treatment protocol, product volumes, product placement, injection technique, and post-injection care. The jawline is best treated using a conservative approach involving low product volumes and under-correction as opposed to over-correction because of the high G′ of HA_{SHA}. Proposed injection would be via a 25G cannula into the subcutaneous layer. The angle of the jawline may also be strengthened/widened with a deeper on periosteum injection. Care should be taken as the product has only recently received market approval and this is an off-label area.

TABLE 2.

Expert Recommendations on Treatment of the Chin With HA_{SHA}	
	Expert Recommendation
Treatment Aims	Following facial assessment, general treatment aims should include a correction of bone support, an improvement in the projection and/or elongation of chin appearance (in proportion to the face overall), and contouring to improve the projection of a receded chin. For a traditionally feminine appearance the focus is on rounding the chin, and for a traditionally masculine appearance the focus is on squaring/widening the chin.
Treatment Area	The midline and either side of the midline of the chin, within the mid to lower third of the mandible.
Patient Expectations	Natural looking improvements in chin shape, projection, and profile to improve overall appearance. Patients may describe themselves as having a 'weak chin' or noting a lack of definition to their lower face.
Target Patient	Patients who desire augmentation, reshaping, or correction of chin retrusion and prefer a non-surgical option with rapid recovery.
Undesirable Patient Characteristics	Post-surgical patients, poor skin elasticity, thin skin.
Choice of Product	Restylane Shaype® is an appropriate HA filler for chin augmentation because of its gel characteristics, precise projection, moldability, long-lasting effect and documented efficacy, and safety for facial aesthetic indications.
Pre-Treatment Counselling	Counselling patients on the potential occurrence of pain is helpful to prepare them for the procedure.
Injection Approach	Mark the midline of the chin and the horizontal thirds. When a wider chin is desired for a traditionally masculine appearance, it is also helpful to mark the vertical medial canthal lines.
Injection Procedure	Insert needle perpendicular to the skin until it touches the periosteum; aspirate; slowly inject product to the appropriate region; massage and mold the area to the ideal shape.
Injection Technique	Use a bolus technique with 1 to 4 injection points depending on the approach and facial anatomy.
Product Volumes	1-2 mL at first treatment and up to an additional 1-2 mL if touch-up is needed. Aim to undertreat rather than overtreat the area and take a staged approach for optimal results.
Product Placement	Inject on the periosteum below the deep mental fat pad and the mentalis muscle.
Needle/Cannula	Recommended sizing is 27G ultra-thin wall x 19 mm needle (co-packed in carton). Injection placement on bone using a cannula is considered an advanced technique for experienced injectors.
Post Injection Care	Routine standard of care. If the treated area is swollen directly after injection, apply an ice pack with adequate protective cloth to the site for a short period. Gauze or other materials can also be used to protect the skin from direct thermal injury. Use ice with caution if the area is still numb from anesthetic to avoid thermal injury.
Safety Alerts	Vascular structures in the area – aspirate and hold for >5 seconds and, if there is no sign of blood, proceed with injection. Pain and other adverse events may be minimized by using smaller injection volumes.

Based on individual patient needs, injectors may use a holistic approach to optimize the lower face and balance the full face using a combination of products with different rheological properties. This holistic approach includes, in addition to treatment of the chin, the jawline, midface including the piriform fossa, and pre-jowl.

CONCLUSION

Experts recommend using HA_{SHA} for treatment in the chin area due to its high strength/firmness that allow for a greater correction/projection/contouring with lower injection volumes. This is particularly beneficial for patients with pronounced chin retrusion. HA_{SHA} also offers a long lasting effect and good overall safety. Depending on the patient's needs and the aim of treatment, different approaches and injection techniques should be applied. For a traditionally feminine appearance, the focus should be on rounding the chin, while for a traditionally masculine appearance, squaring or widening the chin is preferred. Additionally, contouring the chin can improve the projection of a receded chin, and elongation of the chin is to be used to balance the middle and lower thirds of the face. In some cases, the best approach is to use a combination of these techniques. In addition to treatment of the chin, the expert panel also recognized the jawline as a potential area amenable to treatment with HA_{SHA} in real-world practice.

Recommendations by the expert panel are summarized in Table 2. These recommendations aim to provide clinical guidance on best practice use of HA_{SHA}. Further clinical experience will help refine our understanding and optimize the use of this promising new product in our therapeutic armamentarium.

DISCLOSURES

Andreas Nikolis is a paid consultant, speaker, and clinical trial investigator for Galderma, Allergan Aesthetics, Prollenium, and Merz. Katie Beleznay is a paid consultant, speaker, and/or clinical trial investigator for Galderma, Allergan Aesthetics and L'Oreal. Vince Bertucci is a paid consultant, speaker, and/or clinical trial investigator for Galderma, Allergan Aesthetics, Caliway Biopharmaceuticals, Clarion, Cutera, L'Oreal, Medytox, Merz, Prollenium, Revance and Teoxane. Lisa Kellett is a paid consultant, speaker, advisory board member and clinical investigator for Galderma, Merz, Allergan, AbbVie, Cynosure

and Clarion. Andrei Metelitsa is a paid consultant, speaker, and clinical trial investigator for Galderma and Allergan Aesthetics. Kucy Pon is a paid consultant and speaker for Galderma and Allergan Aesthetics. Jason K Rivers is a paid advisory board member and clinical trial investigator for Galderma; advisory board member, speaker bureau member and clinical trial investigator for Allergan Aesthetics; advisory board member and paid consultant for Bausch Health; advisory board member, speaker bureau member, paid consultant and investigator for Leo Pharma; investigator for Medytox; consultant for MetaOptima Technology Inc; investigator for Pfizer; investigator for SaNOtize; founder, stockholder of Riversol Skin Care Solutions Inc. Jennifer Salsberg is a paid consultant, speaker and/or advisory board member for Galderma and Merz. Hani Sinno is a paid consultant to Galderma, Fillmed and Hugel. Desislava Lazarova is an employee at Galderma, Zug, Switzerland. Torun Bromée is an employee at Galderma, Uppsala, Sweden.

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ORIGINAL ARTICLE

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Early Acne Improvements With Fixed-Combination Topical Therapy: Analysis of the First Four Weeks of Treatment

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*Ortho Dermatologics is a division of Bausch Health US, LLC

ABSTRACT

Background: Acne treatment can take weeks to deliver noticeable improvements, which may diminish patients' perception of treatment effectiveness and undermine treatment adherence. Combination topical treatments that target multiple acne pathophysiological pathways are more efficacious than topical monotherapies, and simplifying combination treatment by delivering multiple active ingredients as fixed combinations may improve adherence.

Methods: This review provides an overview of efficacy with 4 weeks of treatment in pivotal trials of fixed-combination topical treatments for acne. Outcomes assessed were reductions from baseline in inflammatory (IL) and noninflammatory lesions (NIL) and treatment success (≥2-grade reduction in global acne severity score and clear/almost clear skin).

Results: Data were compiled for 7 acne topicals, comprising fixed combinations of adapalene (ADAP), benzoyl peroxide (BPO), clindamycin phosphate (CLIN), and tretinoin (TRET). At week 4, lesion reductions from baseline ranged from 32 to 54% (IL) and 25 to 45% (NIL), while rates of treatment success ranged from 3 to 12%. Overall, efficacy was greatest with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel (IL: 54-55%; NIL: 43-45%; treatment success: 8-12%), followed by combinations of ADAP/BPO (IL: ~42-48%; NIL: ~38%; treatment success: 4-~7%).

Conclusions: In clinical trials of topical fixed-combination formulations, triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel yielded greater lesion reductions and rates of treatment success after 4 weeks of treatment than dyad combinations. Even greater differences may be expected with real-world world use, as early improvements may bolster treatment adherence and long-term outcomes.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory skin disease affecting approximately 85% of individuals aged 12 to 24 years.[1-3] Even mild acne can result in long-lasting dyspigmentation and scarring, which may be more bothersome than the acne itself and have profound impacts on psychosocial functioning and quality of life.[4-6] Early and aggressive treatment can be initiated with the twin goals of reducing lesion count and preventing the formation of new lesions in the near term, and mitigating long-term sequelae and associated morbidity.[1,7,8]

Acne treatment can take many weeks before any improvement is observed, and maximal improvement may take several months. This delay presents a frustrating challenge; prolonged time to visible improvement can diminish patients' perception of treatment effectiveness and undermine treatment adherence, further impairing treatment efficacy.[9-11] Medications that deliver rapid initial improvements may encourage continued use, providing the best opportunity for acne resolution.

Efficacy in acne treatment can be enhanced by combining active ingredients to target multiple pathophysiological mechanisms. Combination therapy is more efficacious than monotherapy[12,13] and is recommended by the American Academy of Dermatology (AAD).[2] In addition to improving long-term efficacy, combination treatment yields greater lesion

reductions versus monotherapy with as little as 4 weeks of treatment.[14] Although such early improvements may foster treatment adherence and long-term treatment outcomes, there may be a tradeoff between improved efficacy and decreased adherence due to the increased complexity of the treatment regimen.[9] Providing multiple active ingredients as fixed combinations decreases treatment complexity, which improves both treatment adherence and efficacy.[15]

Several fixed-combination topical products have been approved for acne, including various concentrations of adapalene (ADAP), benzoyl peroxide (BPO), clindamycin phosphate (CLIN), erythromycin (ERYTH), and/or tretinoin (TRET) (Figure 1).[16] The purpose of this review is to provide an overview of early acne improvements with fixed-combination topical treatments by summarizing efficacy after 4 weeks of treatment in pivotal clinical trials.

MATERIALS AND METHODS

Efficacy data for fixed-combination topical treatments were gathered from United States Food and Drug Administration (FDA) medical reviews, prescribing information, and/or publications of pivotal phase 2 and phase 3 trials. For the only triple-combination formulation (CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel), data from a nonpivotal phase 2 study that included dyad combination treatment arms were also included. Analysis was limited to topical therapies for which week 4 data were reported for inflammatory lesion reductions, noninflammatory lesion reductions, or improvement in acne global severity scores. For acne lesions, reported mean percent changes from baseline were compiled when available. Otherwise, absolute lesion counts at baseline and mean lesion reductions at week 4 were used to calculate an estimated percent change from baseline.

Rates of treatment success were compiled for all studies that employed either the Evaluator's Global Severity Score or the Investigator's Global Assessment, which are considered variations of the same scale with different names.[33] Treatment success was defined as the percentage of participants achieving a ≥2-grade reduction from baseline and a score of 0 ("clear skin") or 1 ("almost clear skin"). This definition is consistent with 2018 FDA guidance on defining treatment success in acne clinical trials.[34] Studies in which treatment success was defined only as clear or almost clear skin (score of 0 or 1) were included if all enrolled participants had moderate or severe acne (score of 3 or 4)

FIGURE 1. Fixed-combination topical formulations for the treatment of acne.

Fixed-combination formulations	Clinical trial identifier or study name	
CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel Cabtreo® (Ortho Dermatologics)[17,18]	Phase 2: NCT03170388[a] Phase 3[b]: NCT04214639; NCT04214652	
ADAP 0.3%/BPO 2.5% gel Epiduo Forte® (Galderma)[19]	Phase 3: NCT01880320	
ADAP 0.1%/BPO 2.5% gel Epiduo® (Galderma)[20,21]	Phase 2: Study SRE.18094 Phase 3: NCT00422240(SRE.18087)	
CLIN 1.2%/BPO 2.5% gel Acanya® (Bausch Health)[22]	Phase 3[b]: Studies 012 and 017	
CLIN 1.2%/BPO 3.75% gel Onexton® (Bausch Health)[23]	Phase 3: Study V01-ACYC-301	
Clindamycin 1%/BPO 5% gel BenzaClin® (Valeant)[24]	Phase 3: Studies 1 and 2	
TRET 0.1%/BPO 3% cream Twyneo® (Galderma)[25]	Phase 3: Studies SGT-65-04 and SGT-65-05	
CLIN 1.2%/BPO 5% gel Duac® (Steifel)[26]	Studies 1/2/3/4/5	Not included in this analysis; week 4 efficacy data not reported
CLIN 1.2%/TRET 0.025% gel Veltin™ (Almirall)[27]	Study W0265-03	
CLIN 1.2%/TRET 0.025% gel Ziana™ (Bausch Health)[28,29]	Study 1: 7001.G2HP-06-02 Study 2: 7001.G2HP-07-02	
ERYTH 3%/BPO 5% gel Benzamycin® (Bausch Health)[30]	n/a	
ERYTH 3%/BPO 5% gel Aktipak® (Cutanea Life Sciences)[31,32]	Studies 1 and 2	

All treatments were applied once daily except for clindamycin 1%/BPO 5% gel, which was applied twice daily.
[a]This nonpivotal phase 2 study included dyad treatment arms: ADAP 0.15%/BPO 3.1%, CLIN 1.2%/BPO 3.1%, and CLIN 1.2%/ADAP 0.15%, formulated in the same vehicle as the triple-combination product.
[b]This analysis includes data pooled from these studies.
[c]Clindamycin 1% is equivalent to CLIN 1.2%.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; ERYTH, erythromycin; n/a, efficacy data not available; TRET, tretinoin.

at baseline, as they would have had a ≥2-grade improvement to meet this criterion.

Where available, exact values for all treatment outcomes were used in this analysis. In the absence of exact values, percentages were estimated from published figures. In all instances where estimated percent reductions from baseline lesions were used, values in the results below are indicated with a ~ symbol.

RESULTS

Data were compiled from 10 clinical trials of 7 fixed-combination topicals, comprising combinations of ADAP (0.1-0.3%), BPO (2.5-5%), CLIN 1.2%, and TRET 0.1% (Figure 1; for clindamycin 1%/BPO 5% gel, clindamycin 1% is the equivalent of CLIN 1.2%).[17-22,24,25,35] Despite some differences in enrollment criteria, participant demographics, and baseline characteristics were generally similar across studies. The minimum age for inclusion was 9 to 12 years, and the mean ages of participants in active treatment arms were 18 to 21 years. Across studies, most enrolled participants had moderate acne, though 1 study (ADAP 0.1%/BPO 2.5% gel; Study SRE.18094) enrolled participants with mild acne, and one study enrolled equal percentages of participants with moderate and severe acne (ADAP 0.3%/BPO 2.5% gel).

Week 4 Efficacy: Lesion Reductions

Inflammatory Lesions

Inflammatory lesion reductions from baseline to week 4 were reported for all 7 fixed-combination topicals, though data were not reported in the phase 2 trial of ADAP 0.1%/BPO 2.5% gel (Figure 2). Across all active treatment arms, percent reductions from baseline in inflammatory lesions ranged from 32% to 54%. In 7 of the 9 included clinical trials, these reductions were significantly greater than with vehicle (P<0.05); statistical comparisons to vehicle were not reported for 1 study. Overall, greater reductions from baseline were observed with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel than with any of the dyad formulations, although statistical comparisons

FIGURE 2. Inflammatory lesion reductions from baseline at week 4 with fixed-combination topical treatment.

Fixed-combination formulations	Study	Treatment arm	n[a]	Week 4 inflammatory lesion reductions (%)[b]
CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel	Pooled Phase 3[17,35]	CLIN/ADAP/BPO	242	54% ***
		Veh	121	40%
	Phase 2[18,35]	CLIN/ADAP/BPO	146	55% ***
		ADAP/BPO	150	44% ns, ###
		CLIN/BPO	146	48% * #
		CLIN/ADAP	150	46% * ##
		Veh	148	40%
ADAP 0.3%/BPO 2.5% gel	Phase 3[19]	ADAP/BPO	217	~42%[c] ***
		Veh	69	~20%[c]
ADAP 0.1%/BPO 2.5% gel	Phase 3[20]	ADAP/BPO	415	~48%[c] *
		Veh	418	~33%[c]
	Phase 2[21]	ADAP/BPO	149	week 4 inflammatory lesion data not reported
		Veh	71	
CLIN 1.2%/BPO 2.5% gel	Pooled Phase 3[22]	CLIN/BPO	797	~36%[d] ***
		Veh	395	not reported
CLIN 1.2%/BPO 3.75% gel	Phase 3[35]	CLIN/BPO	253	41%[e]
		Veh	245	23%
Clindamycin 1%/BPO 5% gel	Phase 3[24,f]	CLIN/BPO	120	~32%[g] ***
		Veh	120	lesion count increased by 7%[g]
TRET 0.1%/BPO 3% cream	Phase 3 (Study 1)[25]	TRET/BPO	281	~41%[g] ***
		Veh	143	~29%[g]
	Phase 3 (Study 2)[25]	TRET/BPO	290	~38%[g] ns
		Veh	144	~37%[g]

Intratrial comparisons: *P<0.05, ***P≤0.001 vs vehicle. ns, not significant vs vehicle. #P<0.05, ##P<0.01, ###P≤0.001 vs CLIN/ADAP/BPO.
Treatment arms for which week 4 data were not reported are indicated by gray text.
[a]Intent-to-treat populations.
[b]Mean or least squares mean percent reductions from baseline are presented for all treatments except ADAP 0.1%/BPO 2.5%, for which median percent reductions are presented.
[c]Value was estimated from the published figure.
[d]Population-level percent reduction in lesion count was calculated from a mean absolute change at week 4 divided by a mean count at baseline; the P-value reflects the absolute change.
[e]Statistical significance was not reported.
[f]In a second pivotal study,[36] absolute reduction from baseline to week 4 in inflammatory lesions was significantly greater for CLIN/BPO vs vehicle (P≤0.022); however, the percent reduction could not be calculated because baseline count was not reported.
[g]Population-level percent reduction in lesion count was calculated from a mean absolute change at week 4 (estimated from a figure) divided by a mean count at baseline; P-values reflect the absolute change.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; FDA, United States Food and Drug Administration; ns, not significant; TRET, tretinoin; Veh, vehicle.

could not be made across clinical trials. However, in the phase 2 study of CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel, lesion reductions were significantly greater than for all dyad combinations of the 3 active ingredients ($P<0.05$), and lesion reductions with the ADAP 0.15%/BPO 3.1% dyad were similar to those observed with the commercially available ADAP 0.1%/BPO 2.5% and ADAP 0.3%/BPO 2.5% dyads (42-48%).

Noninflammatory Lesions

Noninflammatory lesion data were available for all fixed-combination topicals except clindamycin 1%/BPO 5% gel (Figure 3). In general, the pattern of noninflammatory lesion reductions from baseline to week 4 was similar to that of inflammatory lesions. Across the 9 included clinical trials, percent reductions from baseline in noninflammatory lesions ranged from 25% to 45% with active treatments. In 8 of the 9 trials, these reductions were significantly greater than with vehicle ($P<0.05$); statistical comparisons were not reported for the final study. As with inflammatory lesions, percent reductions from baseline in noninflammatory lesions were greater with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel than with any of the dyad formulations.

Week 4 Efficacy: Treatment Success

Treatment success data were reported in 7 clinical trials covering 5 of the 7 fixed-combination topicals (Figure 4). Across all trials, the percentage of participants achieving treatment success at week 4 with active treatments ranged from 4% to 12%. These rates were significantly greater than with vehicle for triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel (phase 2 and phase 3 studies) and for ADAP 0.1%/BPO 2.5% gel (phase 3 study; $P<0.05$); statistical comparisons were not reported for 1 study. Overall, treatment success rates were greater with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel than with any of the dyad formulations.

FIGURE 3. Noninflammatory lesion reductions from baseline at week 4 with fixed-combination topical treatment.

Fixed-combination formulations	Study	Treatment arm	n[a]	Week 4 noninflammatory lesion reductions (%)[b]
CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel	Pooled Phase 3[17,35]	CLIN/ADAP/BPO	242	45% ***
		Veh	121	32%
	Phase 2[18,35]	CLIN/ADAP/BPO	146	43% ***
		ADAP/BPO	150	38% **
		CLIN/BPO	146	33% ns, ###
		CLIN/ADAP	150	38% ***
		Veh	148	29%
ADAP 0.3%/BPO 2.5% gel	Phase 3[19]	ADAP/BPO	217	~38%[c] ***
		Veh	69	~19%[c]
ADAP 0.1%/BPO 2.5% gel	Phase 3[20]	ADAP/BPO	415	~38%[c] *
		Veh	418	~27%[c]
	Phase 2[21]	ADAP/BPO	149	31% *
		Veh	71	21%
CLIN 1.2%/BPO 2.5% gel	Pooled Phase 3[22]	CLIN/BPO	797	~25%[d] ***
		Veh	395	not reported
CLIN 1.2%/BPO 3.75% gel	Phase 3[35]	CLIN/BPO	253	27%[e]
		Veh	245	19%
Clindamycin 1%/BPO 5% gel	Phase 3[24,f]	CLIN/BPO	120	week 4 noninflammatory lesion data not reported
		Veh	120	
TRET 0.1%/BPO 3% cream	Phase 3 (Study 1)[25]	TRET/BPO	281	~38%[f] ***
		Veh	143	~28%[f]
	Phase 3 (Study 2)[25]	TRET/BPO	290	~32%[f] *
		Veh	144	~24%[f]

Intratrial comparisons: *$P<0.05$, **$P<0.01$, ***$P\leq0.001$ vs vehicle. ns, not significant vs vehicle. ###$P\leq0.001$ vs CLIN/ADAP/BPO.
Treatment arms for which week 4 data were not reported are indicated by gray text.
[a]Intent-to-treat populations.
[b]Mean or least squares mean percent reductions from baseline are presented for all treatments except ADAP 0.1%/BPO 2.5%, for which median percent reductions are presented.
[c]Value was estimated from the published figure.
[d]Population-level percent reduction in lesion count was calculated from a mean absolute change at week 4 divided by a mean count at baseline; the *P*-value reflects the absolute change.
[e]Statistical significance was not reported.
[f]Population-level percent reduction in lesion count was calculated from a mean absolute change at week 4 (estimated from a figure) divided by a mean count at baseline; *P*-values reflect the absolute change.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; TRET, tretinoin.

FIGURE 4. Treatment success at week 4 with fixed-combination topical treatment.

FDA-approved topical formulations	Study	Treatment arm	n[a]	Week 4 treatment success, %[b]
CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel	Pooled Phase 3[6,22]	CLIN/ADAP/BPO	242	12%[c] *
		Veh	121	4%
	Phase 2[7,22]	CLIN/ADAP/BPO	146	8% **
		ADAP 0.15%/BPO 3.1%	150	6% *
		CLIN 1.2%/BPO 3.1%	146	3% *ns*, #
		CLIN 1.2%/ADAP 0.15%	150	4% *ns*
		Veh	148	1%
ADAP 0.3%/BPO 2.5% gel	Phase 3[8]	ADAP/BPO	217	4% *ns*
		Veh	69	2%
ADAP 0.1%/BPO 2.5% gel	Phase 3[9]	ADAP/BPO	415	~7%[d] *
		Veh	418	~3%[d]
	Phase 2[10]	ADAP/BPO	149	treatment success defined differently from other studies
		Veh	71	
CLIN 1.2%/BPO 2.5% gel	Pooled Phase 3[11]	CLIN/BPO	797	~8% *
		Veh	395	~2%
CLIN 1.2%/BPO 3.75% gel	Phase 3[22]	CLIN/BPO	253	6%[e]
		Veh	245	4%
Clindamycin 1%/BPO 5% gel	Phase 3[13]	CLIN/BPO	120	treatment success defined differently from other studies
		Veh	120	
TRET 0.1%/BPO 3% cream	Phase 3 (Study 1)[14]	TRET/BPO	281	~6%[d] *ns*
		Veh	143	~3%[d]
	Phase 3 (Study 2)[15]	TRET/BPO	290	~6%[d] *ns*
		Veh	144	~6%[d]

Intratrial comparisons: *$P<0.05$, **$P<0.01$ vs vehicle. ns, not significant vs vehicle. #$P<0.05$ vs CLIN/ADAP/BPO.
Treatment arms for which week 4 data were not reported are indicated by gray text.
[a]Intent-to-treat populations.
[b]≥2-grade reduction in Evaluator's Global Severity Score and a score of 0 ("clear") or 1 ("almost clear").
[c]*P*-value from a logistic regression (using Firth's Penalized Likelihood) with factors of the treatment group and analysis center. Values have been adjusted for multiple imputation using the Markov Chain Monte Carlo method.
[d]Value was estimated from the published figure.
[e]Statistical significance was not reported.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; FDA, United States Food and Drug Administration; TRET, tretinoin; Veh, vehicle.

DISCUSSION

Acne treatments that deliver early visible improvements may encourage treatment adherence and bolster overall treatment effectiveness. Among 7 fixed-combination topicals, clinical trial efficacy after 4 weeks of treatment, measured as treatment success or inflammatory/noninflammatory lesion reductions, was greatest for triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel, followed by fixed-combination ADAP (0.1% or 0.3%)/BPO 2.5%.

The multifactorial pathogenesis of acne involves epithelial hyperproliferation, changes in sebum production and composition, proliferation of *Cutibacterium acnes*, and inflammation.[37] In a meta-analysis of 221 clinical trials involving 37 acne interventions, topical combination therapies were more efficacious than topical monotherapies[12]; consistent with this, the AAD recommends that topical treatment of acne consist of multimodal therapy combining multiple mechanisms of action.[2] Among acne topicals, CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel is the only formulation with active ingredients that target 3 of the 4 acne pathophysiological pathways; ADAP normalizes epithelial proliferation, CLIN and BPO reduce *C acnes* viability, and all 3 active ingredients have anti-inflammatory properties.[2,38-40] The enhanced benefit of triple-combination therapy over dyad combination therapy is evident in data from phase 2 and two phase 3 clinical trials.[18,41] With 12 weeks of once-daily treatment, CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel yielded >70% reductions in inflammatory and noninflammatory lesions and treatment success in ~50% of participants; these results are greater than have been observed in clinical trials of any fixed-combination dyad formulation. The findings of greater lesion reductions and treatment success rates at week 4 are consistent with the greater 12-week efficacy of CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel compared with other fixed-combination topicals.

Acne clinical trials represent a best-case scenario for treatment adherence and subsequent efficacy; provision of free medication, compensation for participation, and frequent follow-up (eg, every 4 weeks) can all be expected to promote treatment adherence. As a result, lack of efficacy early in a clinical trial may be less likely

to result in noncompliance with the treatment protocol than with real-world use. Consistent with this, in clinical trials of CLIN 1.2%/BPO 3.75% and CLIN 1.2%/ADAP 0.15%/BPO 3.1% gels, treatment compliance, defined as not missing >5 consecutive applications and applying 80% to 120% of expected applications, was >90%.[18,35,41] Thus, acne improvements observed in clinical trials likely reflect the maximal therapeutic effects that can be expected with a particular medication.

In contrast, real-world treatment adherence is more susceptible to lack of early improvements and the perception of ineffectiveness,[9,11,42,43] with some clinical impressions suggesting that adherence begins to decline as early as 3 weeks after treatment initiation.[44] Consequently, overall adherence is considerably lower than in clinical trials, with many studies reporting adherence rates of 50% or less[10,43,45,46] and particularly low rates among children and adolescents.[47] Long-term effectiveness will therefore suffer, as unused drugs cannot provide any clinical benefit. Unfortunately, real-world data on adherence and effectiveness with fixed-combination topical acne treatments are limited, particularly for recently approved formulations. However, there are some data from clinical studies showing greater adherence and/or efficacy with fixed-combination topicals compared with separate applications of the active ingredients.[15,48]

Although all assessed fixed-combination topicals had some degree of efficacy with 4 weeks of treatment, there are few predictors of how these improvements might translate to real-world perception of efficacy. Inflammatory lesions may be particularly impactful on patients' perception of their acne, as they are more visible from a distance.[49] In one meta-analysis of data from 7 clinical trials with >4000 participants, cutoff points were determined for inflammatory lesion reductions that corresponded to participants' subjective ratings of acne improvement.[50] Based on these cutoffs, "moderate" acne improvement was associated with inflammatory lesion reductions of 34.71% to 61.57%. Thus, acne improvement at week 4 would be considered "moderate" for all fixed-combination treatments assessed, with the exception of clindamycin 1%/BPO 5% gel (<34.71%; "no improvement"; Figure 2). Given the importance of such early efficacy, improvement with as little as 2 weeks of treatment was only observed with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel ("moderate" inflammatory lesion reductions of 35.9-36.5%) in trials for which data are available.[17,18,51] Moreover, in a responder analysis of participants in the phase 2 and phase 3 studies of the triple-combination, >50% of participants experienced at least a one-third reduction in inflammatory lesions at week 2.[52]

Comparison of treatment efficacy across clinical trials is limited by factors such as participant demographics, baseline disease characteristics, and methodological differences. Although participant demographics were generally consistent across the studies included here, there were some differences in the percentages of participants with moderate versus severe acne. Unfortunately, many studies were excluded from this comparison owing to differences in the criteria for treatment success, and several topical fixed combinations were excluded altogether for not having data reported at week 4, limiting the generalizability of the results. Although many studies reported percent lesion reductions from baseline as exact values, some reported reductions only in figures or as absolute changes from baseline, requiring estimation of percent changes. Despite these differences, the pattern of results across treatments was highly consistent for inflammatory and noninflammatory lesion reductions and treatment success. Thus, the overall trends observed may still be considered reliable indicators of differences in early efficacy across treatments.

Analysis of early acne improvements provides insight into only 1 of many aspects of acne treatment that may impact treatment adherence. The prolonged treatment duration required for acne clearance may discourage adherence,[9] and plain forgetfulness accounts for up to half of nonadherence,[53] though the effects of both may be mitigated by appropriate expectation setting and frequent follow-up.[9,54] Treatment-related irritation may also cause patients to stop using their medication.[55] For all formulations included in this assessment, treatment-related adverse events and safety/tolerability symptoms were similar, the majority of which were transient and of mild-to-moderate severity. Patients are more likely to use topicals that they prefer,[54] which is affected by factors such as cosmetic characteristics of the vehicle used and overall ease of use.[56,57] Both primary and secondary adherence suffer as additional separate products are included in a treatment regimen,[9,58] though this may be circumvented by delivering them as fixed combinations.[15] Consistent with this, participants in studies of both CLIN 1.2%/ADAP 0.15%/BPO 3.1% and ADAP 0.1%/BPO 2.5% gels expressed preference for the fixed-combination formulations over monad formulations.[20,59] Furthermore, in 2 small studies, adherence to daily treatment with CLIN 1.2%/TRET 0.025% gel was better than with separate applications of the active ingredients,[15] and adherence to treatment with once-daily triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% was better than separate applications of CLIN 1.2% and ADAP 0.1%/BPO 2.5% gels.[48]

CONCLUSION

Early improvements in acne treatment may encourage treatment adherence and overall treatment outcomes. Among topical fixed-combination formulations, triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel yielded greater lesion reductions and rates of treatment success after 4 weeks of treatment than did dyad combinations. Even greater differences may be expected with long-term real-world world use, given the poor adherence to complex topical regimens in real-life settings.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Integrating Dermocosmetic Therapy for Acne: Addressing Severity Levels in Real-Life Experiences

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ABSTRACT

Background: Acne is prevalent in approximately 80% of individuals aged 11 to 30 years, with scarring occurring in about 40% of cases. Early and sustained treatment is crucial for preventing acne scarring, regardless of severity.

Objectives: The objective of this study was to evaluate skin tolerability and patient compliance after combining a specific dermatologic routine with pharmacological therapy in patients affected by different degrees of acne.

Methods: A comprehensive treatment approach was developed, combining pharmacological therapies in line with established guidelines and a supportive dermocosmetic routine. This routine included a gentle soap-free cleansing emulsion, a moisturizing cream containing glycerin, niacinamide, panthenol, and photoprotection. An anonymous questionnaire was administered to 28 patients (ages 14-31, male and female) to assess their satisfaction and adherence to the treatment plan.

Results: Patient adherence to the therapeutic protocol was found to be essential for achieving expected outcomes. The integration of a specific dermocosmetic routine significantly reduced the risks of erythema, dryness, sensitivity, and retinoid dermatitis, which can lead to treatment interruption and failure. The majority of patients reported high levels of satisfaction with the dermocosmetic products, reinforcing their role in supporting pharmacological treatment.

Conclusion: A holistic approach that integrates personalized dermocosmetological prescription to support pharmacological treatment in the different degrees of acne severity significantly enhances patient adherence and satisfaction, which is essential for successful acne management. By prioritizing adherence to treatment protocols and supporting them with an effective dermocosmetic routine, this strategy ensures better overall outcomes in managing acne.

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INTRODUCTION

Acne affects approximately 80% of individuals aged 11 to 30 years, with scarring occurring in about 40% of cases.[1,2] Early and sustained treatment is crucial for preventing acne scarring in all patients, regardless of acne severity. The three primary degrees of acne—mild/papulo-comedonic, moderate/papulo-pustular, and severe/nodulocystic—guide therapy guidelines, which recommend retinoids as the cornerstone of management during both acute and maintenance phases. To effectively prevent scar formation, a holistic approach is necessary, aiming for an initial treatment that achieves more than 50% clearance of acne lesions and maintenance therapy to prevent relapses through the continued use of topical treatments. Supplementing a pharmacological therapy involving topical retinoids within an appropriate skincare regimen can significantly improve acne management. Conversely, inappropriate skincare practices may lead to increased irritation related to medications, affect sebum production, and potentially exacerbate acne symptoms. A thorough understanding of overall skin health underscores the importance of implementing comprehensive skincare routines in conjunction with pharmacological treatments. This integrated approach not only aims to optimize treatment outcomes but also fosters patient adherence by minimizing adverse effects and promoting skin well-being. Moreover, patient adherence to the therapeutic protocol is vital at all levels of acne severity to achieve the desired outcomes.

Oral Isotretinoin and Topical Retinoids in Acne Treatment

Oral isotretinoin and topical retinoids (eg, tretinoin, adapalene) or their fixed combinations with benzoyl peroxide can cause significant irritation due to a phenomenon known as "retinoid dermatitis". These retinoids accelerate epidermal cell turnover, leading to thickening of the basal cells in the epidermis and thinning of the corneocyte layer. These changes can alter skin barrier and transepidermal water loss (TEWL).[3] As a result, the skin may become more sensitive, particularly during the initial weeks of treatment, leading to various side effects.

The most common signs of sensitive skin are closely linked to impaired barrier function. These include a weakened skin barrier characterized by decreased levels of lipids and proteins,

which leads to dryness and increased water loss due to enhanced skin permeability. This compromised barrier can also result in roughness stemming from abnormal desquamation. In addition to these physical signs, individuals with sensitive skin may experience unpleasant sensory symptoms in response to external stimuli that normally should not provoke such sensations. These symptoms often manifest as irritation, which can include sensations of itching, burning, and stinging, frequently triggered by inflammation. Moreover, affected individuals may report tightness and general skin discomfort, stemming from a neurosensory response.

The high risk of side effects associated with acne therapies can significantly contribute to nonadherence to treatment regimens. To address this issue, the daily use of a dermocosmetic moisturizing cream and a gentle cleanser as adjunctive therapy can be highly beneficial. These products help to minimize irritation, reduce dryness and desquamation, and enhance skin barrier function, ultimately improving patient adherence and leading to better treatment outcomes.

Support from dermocosmetic routine is crucial for maintaining high levels of patient compliance and mitigating the risks of redness, dryness, sensitive skin, and retinoid dermatitis. If left unaddressed, these side effects can result in treatment interruptions and therapeutic failure, underscoring the importance of integrating an appropriate dermocosmetic regimen into acne management plans. By alleviating the discomfort associated with acne therapies, we can foster a more positive treatment experience and encourage patients to remain committed to their prescribed regimens.

Patient Treatment Overview

In this study, a total of 28 patients were treated, including 13 males (aged 14-20 years) and 15 females (aged 15-31 years), all affected by acne of varying severity. The acne was classified into three categories: mild cases, including comedonal acne and seborrhea; moderate cases comprised papular-pustular acne; and severe cases were characterized by nodular-cystic acne and atrophic scars. Treatment was administered over a six-month period in a personal protocol for acne management.

For patients with mild acne, topical therapies were employed, including retinoids or fixed combinations of retinoids and benzoyl peroxide, such as adapalene 0.3%/BPO 2.5%, as well as salicylic acid and alpha hydroxy acids (AHAs). In moderate acne patients, topical treatments consisted of retinoids (eg, adapalene, trifarotene), benzoyl peroxide, fixed combinations, and antibiotics like clindamycin. Systemic hormonal therapy was provided for female patients when necessary. In severe cases, oral isotretinoin and oral hormonal therapy were prescribed alongside topical fixed combinations.

Throughout the therapy duration, a daily dermocosmetic regimen was followed by all patients to support pharmacological treatment. This regimen included the use of a gentle cleanser, specifically Cetaphil® Gentle Skin Cleanser (Galderma), and a moisturizing cream, Cetaphil® Moisturizing Cream (Galderma), which contains niacinamide, panthenol, and glycerin. Instructions were given for the gentle cleanser to be used twice daily, for the moisturizing cream to be applied during the daytime, and for a sunscreen with SPF 50 suitable for oily skin to be chosen by each patient. In the nighttime, the moisturizing cream was applied at alternate night with pharmacological topical treatment

The aim of this work is to evaluate skin tolerability and PATIENT compliance after combining a specific dermocosmetic routine with pharmacological therapy in patients affected by different degrees of acne. An anonymous questionnaire (Figure 1) was utilized to gather this information. The ultimate goal is to enhance adherence to the comprehensive therapy while reducing dryness, erythema, redness, and burning sensations, thus minimizing the risk of retinoid dermatitis associated with both topical retinoids and oral isotretinoin.

MATERIALS AND METHODS

Study Design

A total of 28 patients were treated for acne over a six-month period, classified into three categories based on severity: mild, moderate, and severe. The mild acne group consisted of 8 patients (6 females and 2 males), the moderate acne group included 11 patients (5 females and 6 males), and the severe acne group comprised 9 patients (4 females and 5 males; Tables 1-3). Pharmacological treatments prescribed included not only topical treatments but also oral treatments (such as isotretinoin or hormonal treatments) in accordance with established acne management guidelines.[4]

Dermocosmetic Regimen

A daily skincare routine was integrated with pharmacological therapies based on acne treatment guidelines. This regimen included a gentle, soap-free, and hypoallergenic cleansing emulsion (Cetaphil® Gentle Skin Cleanser, Galderma), which was used twice daily. The emulsion contains key ingredients such as glycerin, panthenol, niacinamide, pantolactone, and sodium cocoyl isethionate. It is a fragrance-free, non-comedogenic formulation, and suitable for dual-mode use (with or without rinsing).

Patients also applied a hydrating cream (Cetaphil® Moisturizing Cream, Galderma), enriched with sweet almond oil, glycerin, niacinamide, and panthenol, along with an oil-free sunscreen with SPF 50 (selected by the patient). This dermocosmetic routine was maintained for 6 months alongside comprehensive acne treatment.

The integration of this daily dermocosmetic routine aimed to optimize the therapeutic effects of pharmacological treatments while addressing common side effects such as dryness, irritation, and compromised skin barrier function, thus promoting better overall adherence to the acne treatment protocol. The synergistic effects of the cleanser and moisturizer are anticipated to contribute significantly to the overall success of acne management in patients.[5]

Efficacy of Cleansing Emulsion

The cleansing emulsion used by the patients during the treatment period is a fragrance-free, soap-free, hypoallergenic, and non-comedogenic formulation, which makes this gentle cleanser particularly suitable for sensitive and acne-prone skin. Its dual-mode use allows for application with or without rinsing, offering flexibility depending on the patient's preference and skin condition. The formulation preserves the skin barrier even after repeated washing, effectively increasing skin hydration after a single application, regardless of rinsing. Clinical studies have shown that it reduces dryness and skin roughness, as well as minimizes skin irritation after 28 days of continuous use.

Efficacy of Moisturizing Cream

The moisturizing used by the patients during the treatment period is formulated with ingredients such as glycerin, dicaprylyl ether, dimethicone, glyceryl stearate, cetyl alcohol, and some plant-derived oils, including sunflower seed oil and sweet almond oil. This cream is non-comedogenic and free from added fragrances. Alterations in skin barrier function, caused by intrinsic or extrinsic factors, can lead to increased transepidermal water loss (TEWL), dryness, itching, and desquamation. Recovery of the barrier function is crucial, and adequate moisturizers provide significant support. The moisturizing cream was shown to restore the skin barrier within seven days, improve skin hydration for up to 48 hours after a single application, and significantly reduce dryness and skin roughness after 14 days of use.[6,7]

Active Ingredients in Dermocosmetic Products

Niacinamide is a key dermocosmetic ingredient that enhances the production of all essentials classes of serine palmitoyltransferase, the rate-limiting enzyme in sphingolipid synthesis, thus improving barrier function and hydration. It effectively reduces TEWL and strengthens the skin barrier while enhancing keratinocyte differentiation and proliferation. For sensitive skin, niacinamide is known to reduce inflammation (PGE-2, cytokines), alleviate redness, and minimize dryness, demonstrating high tolerability.[8]

Panthenol containing are able to promote superficial wounds and restore damaged epithelium by improving skin barrier repair following induced . It also reduces TEWL and strengthens the skin barrier. As a humectant and emollient, panthenol improves cutaneous hydration and provides moisturizing effects as active ingredient. For sensitive skin, it reduces inflammation (PGE-2), enhances skin roughness, and alleviates redness, irritation, itchiness, and dryness, effectively soothing the skin.

Glycerin is another essential ingredient that reduces TEWL and aids in maintaining and improving epidermal barrier function. It serves as an emollient, enhancing stratum corneum hydration and reducing dryness.

The synergy between the gentle emulsion cleanser and the moisturizing cream, enhanced by these three combined ingredients, leads to significant improvements in skin barrier function and hydration, promoting overall skin health and comfort. Niacinamide plays a crucial role in enhancing skin health by boosting ceramide production.

It increases the expression of filaggrin and involucrin in skin keratinocytes,[9] both of which are vital for skin barrier integrity. Involucrin, in particular, is a protein that contributes to the formation of the skin's protective outer layer, aiding in keratinization and enhancing barrier function.

Therapy According to Acne Severity

Mild Acne: In the mild acne category (6 females and 2 males), the treatment plan lasted for 6 months and focused solely on topical therapies. No oral therapy was administered. Patients followed a regimen that included a gentle cleansing emulsion, used twice daily, a moisturizing cream, and sunscreen with SPF 50 for oil control. In the evening, patients alternated between using either an AHA or a fixed combination of adapalene and benzoyl peroxide, along with the moisturizing cream or clindamycin gel at 1%.

Moderate Acne: For the moderate acne group (5 females and 6 males), the treatment lasted 6 months. Some female patients received oral hormonal therapy as part of their pharmacological treatment. The dermocosmetic regimen included a gentle cleansing emulsion applied twice daily, a moisturizing cream, and an oil-control sunscreen with SPF 50. Every night, patients applied the mosturizing cream and alternated between applying either a topical retinoid (adapalene or trifarotene) and clindamycin gel at 1%.

Severe Acne: The severe acne category included 4 females and 5 males, with a comprehensive treatment plan over 6 months. Systemic therapy with oral isotretinoin was prescribed, and some female patients also received hormonal therapy. The topical regimen consisted of a gentle cleansing emulsion, applied twice daily, a moisturizing cream, and sunscreen with SPF 50 for oil control. Nightly care included the moisturizing cream and clindamycin gel at 1%, which were alternated during the first month of treatment.

Evaluation of Tolerability and Compliance

To assess the tolerability and compliance of the combined dermocosmetic and pharmacological therapy, an anonymous questionnaire was administered to all patients at the end of the treatment period. The questionnaire aimed to evaluate the effectiveness of the regimen in reducing dryness, erythema, and irritation, as well as overall satisfaction with the treatment experience. The ultimate goal of the study was to enhance patient adherence to the comprehensive therapy while minimizing the risk of retinoid dermatitis associated with topical retinoids and oral isotretinoin.

RESULTS

The study included a total of 28 participants, comprising 15 females and 13 males, with ages ranging from 14 to 31 years (mean age, 18.6 years). Acne severity among participants varied, with 8 classified as having mild acne, 11 with moderate acne, and 9 exhibiting severe acne. This demographic distribution allowed for a comprehensive analysis of treatment responses across different age groups and levels of acne severity.

Data was collected using a structured, anonymous questionnaire (Figure 1) that assessed a range of factors related to the participants' acne treatment experiences. The questionnaire gathered demographic information, including age and gender. Patients were asked to evaluate different aspects of their overall experience with acne and with the treatment, including an evaluation of the importance of the benefits provided by the dermocosmetic routine used, using a 0—5 scale for some key questions.

FIGURE 1. Acne impact and treatment questionnaire.

Sex: ☐ Female ☐ Male

Age:

1. How much impact does acne have on your social life?

0 (Not relevant) ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 (Very relevant)

2. How satisfied are you with the treatment outcomes?

0 (Not relevant) ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 (Very relevant)

3. What side effects did you experience?

4. How important was the benefit of cosmetic products?

0 (Not relevant) ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 (Very relevant)

5. How do you judge the cosmetic products used?

For questions 1 and 4 (Figure 1), participants rated their experiences on a scale from 0 to 5, where 0 indicated "not relevant" and 5 indicated "very relevant." The questionnaire addressed the impact of acne on social life, satisfaction with treatment outcomes, side effects experienced, the benefit of cosmetic products used, and the relevance of the cosmetic products in their treatment. Side effects were recorded through an open-ended response. This use of a 0—5 scale across the questionnaire facilitated a standardized assessment of participants' perceptions and treatment-related outcomes.

Participants rated their subjective satisfaction for overall treatment OUTCOMES using a numerical scale, ranging from 0= none to 5=optimal, facilitating quantitative analysis. Responses were analyzed to identify trends and correlations between acne severity, adherence to treatment, and the perceived effectiveness of the dermocosmetic regimen.

Impact on Social Life

The perceived impact of acne on patients' social lives varied across different levels of acne severity, reflecting individual experiences with the condition. Among participants affected by mild acne, quite surprisingly, no one assigned the lowest score (0 or 1) to acne impact on their social life. In the moderate acne group, 2 patients rated the impact as slightly relevant (score = 1), while one rated it as moderately relevant (score = 2) and 3 rated it as relevant, assigning a score = 4. In the severe acne group, 3 patients indicated a score of 3 (quite relevant), and 4 patients rated the impact as 4 (relevant). While, surprisingly, one patient (an 18-year-old male) rated the acne impact on his social life as not relevant.

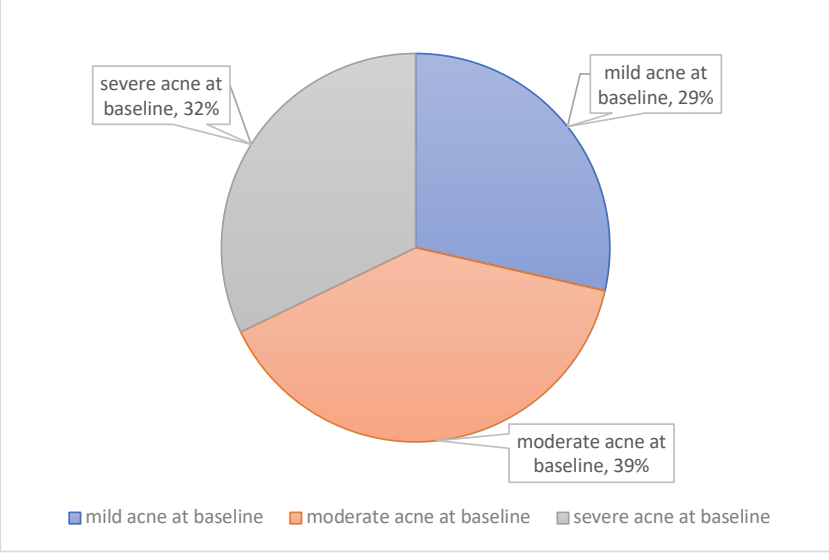
These findings suggest that the perceived impact on social life may be influenced more by subjective factors, such as the psychological characteristics of the patient, rather than by the objective severity of the condition, as observed in this cohort (Figure 3).

Importance of Benefits from the Supporting Cosmetic Routine

The integration of a supportive cosmetic routine was highly rated. None of the participants indicated that its importance was not relevant. One patient rated it slightly relevant (score = 1), and 2 patients found it moderately relevant (score = 2). Additionally, 2 patients affected by mild acne rated it as quite relevant (score = 3), while 14 patients (mainly affected by severe forms of acne) recognized it as relevant (score = 4) and 9 (mainly affected by moderate acne) deemed it very relevant (score = 5). This results in a mean score of 4, underscoring the routine's critical role in enhancing treatment efficacy (Figure 4).

Patient comments, received as open answers to questions in the questionnaire, further support these findings, with several participants describing the products in positive terms. Some

FIGURE 2. Acne severity at baseline.



patients found the products to be "perfect" and "very effective," with one commenting that the products were "very effective to avoid dry skin." Others described the products as "not bothersome" and "helpful in improving skin quality." Several patients expressed strong appreciation, calling the regimen "absolutely essential" for their treatment. These personal evaluations highlight the perceived benefits of the supporting cosmetic routine, emphasizing its role in improving both the physical and emotional aspects of acne treatment.

Satisfaction With Treatment Outcomes

Satisfaction with acne treatment outcomes was predominantly high, with a mean satisfaction score of 4.2. No participants reported none, very low, or quite low satisfaction (scores from 0 to 2). Four participants rated their satisfaction as moderate (score = 3), while 13 indicated high satisfaction (score = 4), and 10 reported optimal satisfaction (score = 5). This distribution indicates that the majority of patients, regardless of the severity of their acne at baseline, experienced positive outcomes

FIGURE 3. Impact of acne on social life: Percentages of patients reporting any level of impact, across all acne severity scores.

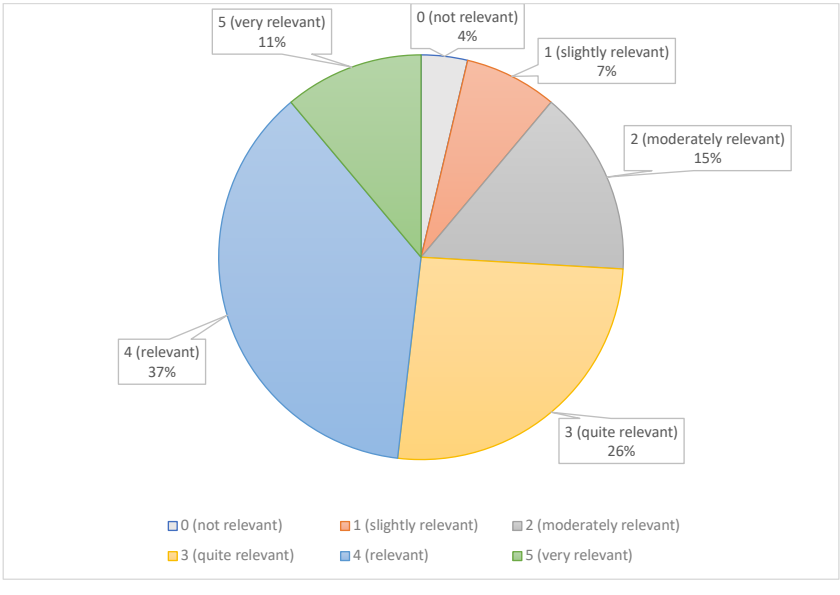
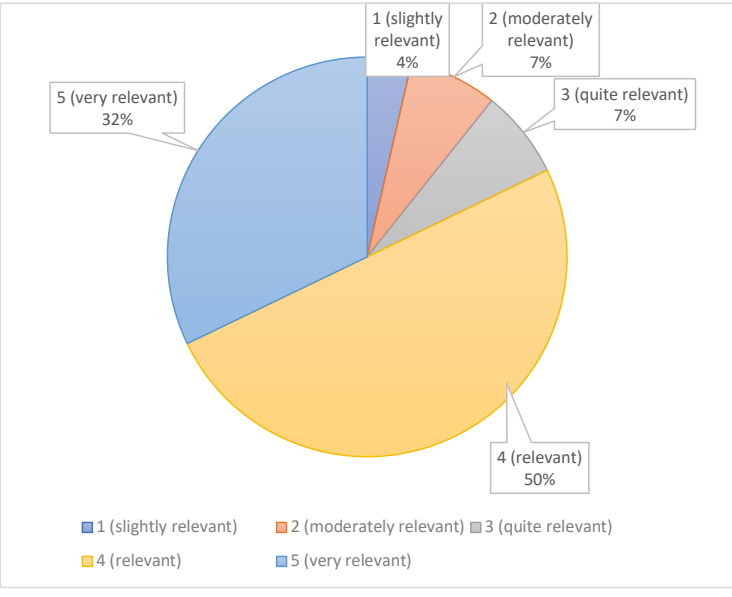


FIGURE 4. Importance of benefits from the supportive cosmetic routine: percentages of patients reporting any level of importance, across all acne severity scores.



from their acne therapies, reinforcing the effectiveness of the combined pharmacological and dermocosmetic approach (Figure 5).

In summary, these findings emphasize that the integration of a supportive cosmetic routine significantly enhances treatment outcomes as far as it concerns acne patients, whatever the baseline disease severity. The high mean scores for both the importance of the benefits provided by the cosmetic routine and the satisfaction for treatment outcomes underscore the vital role of a proper supportive cosmetic routine in improving overall patient experiences in acne management.

DISCUSSION

The findings from this study underscore the critical role of integrating pharmacological therapies with a tailored dermocosmetic regimen in the management of acne. This holistic approach was supported by data collected from 28 participants, consisting of 15 females and 13 males aged 14 to 31 years, classified into mild, moderate, and severe acne

FIGURE 5. Satisfaction with acne therapy: percentages of patients reporting any level of satisfaction, across all acne severity scores.

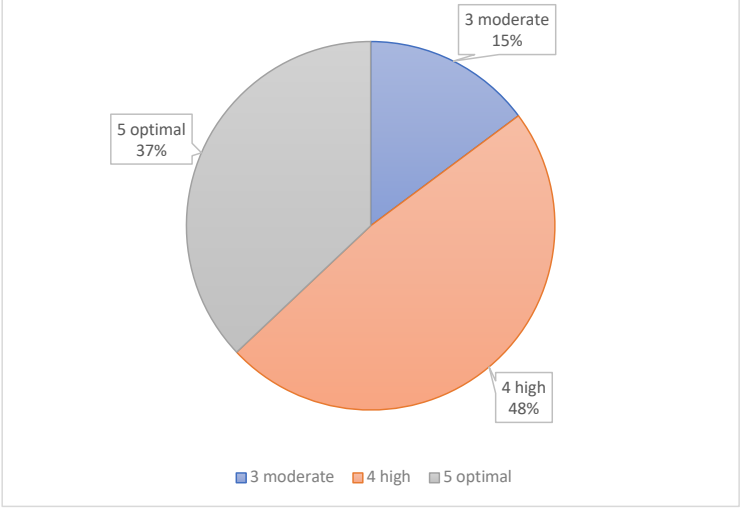


FIGURE 6. Patient responses: summary of individual patient feedback on the acne treatment and supportive cosmetic routine, across all acne severity groups.

Acne Severity Baseline	Impact on Social Life	Number of Patients
MILD 8	0 not relevant	1
MODERATE 11	1 slightly relevant	2
SEVERE 9	2 moderately relevant	4
	3 quite relevant	7
	4 relevant	10
	5 very relevant	3

Importance of Benefits Provided By the Supporting Cosmetic Routine	Number of Patients
0 not relevant	0
1 slightly relevant	1
2 moderately relevant	2
3 quite relevant	2
4 relevant	14
5 very relevant	9

Satisfaction for acne therapy	number of patients
0 none	0
1 very low	0
2 quite low	0
3 moderate	4
4 high	13
5 optimal	10

categories. The results suggest that the perceived impact of acne on social life is influenced more by subjective factors—such as the psychological characteristics of the patient—than by the objective severity of the condition. This was particularly evident in the varying impact scores across different acne severities, indicating that individual experiences and perceptions play a significant role in how acne affects social functioning.

The supportive dermocosmetic regimen, which included a gentle, soap-free cleansing emulsion and a hydrating moisturizing cream enriched with niacinamide, panthenol, and glycerin, was highly rated by participants. With a mean importance score of 4 out of 5, corresponding to a "relevant" importance of the benefits provided by the dermocosmetic routine, the regimen demonstrated its effectiveness in enhancing treatment adherence and mitigating adverse effects associated with pharmacological treatments. Participants also reported high levels of satisfaction FOR their acne TREATMENT OUTCOMES, with a mean SATISFACTION score of 4.2-DEMONSTRATING WIDESPREAD RESULTS. AWARENESS OF the positive RESULTS associated with the combined approach.

By effectively addressing the physical and emotional aspects of acne, this study provides evidence that a comprehensive skincare regimen can significantly enhance treatment adherence and overall patient experiences. The data support the notion that personalized care strategies, which include both pharmacological treatments and supportive dermocosmetics, are essential for optimizing treatment outcomes.

CONCLUSION

This study highlights the importance of prescribing a supportive dermocosmetic regimen alongside pharmacological treatments to improve adherence and outcomes in acne management. The integration of a gentle skin cleanser and a moisturizing cream was well-received by participants, demonstrating high satisfaction and perceived importance. These products not only enhance skin health but also mitigate irritation and dryness, common side effects of acne therapies.

By prioritizing an integrated approach that combines effective cleansing and moisturizing with targeted pharmacological interventions, healthcare providers can significantly improve patient adherence to treatments and overall satisfaction. This strategy not only addresses the physical manifestations of acne but also supports patients' emotional well-being, ultimately leading to better overall treatment outcomes. The positive feedback and high ratings for the supportive regimen reinforce the necessity of personalized skincare solutions in the comprehensive management of acne.

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DISCLOSURES

Dr Magda Belmontesi has no relative financial interests to disclose.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Use of Bovine Xenografts for Nasal Defects After Mohs Micrographic Surgery

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ABSTRACT

Background: Nasal defects after skin cancer excision can often be healed by second intention in certain circumstances.
Objective: We aim to demonstrate the utility of bovine collagen xenografts in supplementing second-intention healing of a variety of nose surgical defects.
Results: Thirty-nine patients underwent Mohs micrographic surgery of the nasal tip (33%), ala (23%), dorsum (31%), sidewall (10%), and root (3%) with the application of bovine collagen xenograft. The average defect size was 1.89 cm^2 (0.36 – 7.5 cm^2). The average time to re-epithelialization was 33 days (range, 11 – 60 days) at a rate of 19.4 days to healing per cm^2 of defect size, which represented an improved time to reepithelialization of over 40% compared to historical controls of second intention healing. Cosmetic outcomes were outstanding or acceptable in 77% of the cases.
Conclusion: Bovine collagen xenografting is a safe and effective method to enhance the second intention of healing Mohs excision defects of the nose, with overall excellent cosmetic results.

J Drugs Dermatol. 2025;24(1):96-99. doi:10.36849/JDD.8634

INTRODUCTION

Nasal defects after Mohs micrographic surgery have a myriad of closure and reconstruction methods, including second intention, split or full-thickness skin grafts, local flaps, and pedicled flaps. Commonly, for superficial and smaller defects of the nose, second-intention healing results in cosmetic outcomes that are arguably superior to that of surgically sutured repairs.[1-3] This is especially true in the concave areas of the nose, such as the nasal sidewall, alar crease, and lateral nasal dorsum, where naturally shadowed contours hide light reflex or pigmentation differences normally revealing of nasal scars.[2] When used for appropriate wounds based on location, size, depth, and patient preference, second-intention healing has many advantages, including decreased overall surgical time, a smaller scar profile, and high levels of patient satisfaction.[4] However, its main disadvantages are prolonged healing time, daily bleeding and drainage from open wounds, and the possibility of wound infection.[5] Biologic dressings, or skin substitutes, are a useful option to overcome these disadvantages of second intention healing, with increasing use on acute surgical wounds to improve healing time, reduce wound complications, and alleviate the healthcare cost of prolonged wound care.

As of the last analysis in 2020, around 76 skin substitutes have been developed and commercially available in the United States.[6] While the majority of these products are designed for use in chronic non-healing wounds, their utility in the acute post-surgical setting has been recognized and increasingly explored.[7-13] Many different classification schemes have been utilized in the literature, categorized by cellular composition (amnion, epithelial, acellular allograft, cellular allograft, xenograft, composites, synthetics) and by intended skin layer replacement (epidermal, dermal, composite epidermal, and dermal).[6] To date, there have not been robust comparisons of products in terms of wound healing efficacy. Therefore, the selection of skin substitutes for regular use on acute surgical wounds is based on physician familiarity, overhead cost of the product, shelf life, insurance coverage, and patient considerations such as the need for frequent return visits for graft reapplication or wound debridement.

The authors have found bovine-derived collagen wound dressing (Puracol®, Medline Industries, Inc; Mundelein, IL) to be a cost-efficient workhorse skin substitute. As a xenograft, Puracol® is bovine-derived type 1 collagen in its native triple-helix formation, consisting of 88.4% collagen.[14] Its affordability,

long shelf-life, and convenience of use gives it distinct advantages over comparative skin substitute products for high-patient volume practice settings with a variety of wound sizes after surgery. It is indicated in use for partial and full-thickness wounds, surgical wounds, vascular wounds, and other surface wounds or abrasions.[15] Available sizes range from 5.1 x 5.7 cm^2 to 20.3 x 20.3 cm^2. Its shelf life is 3 years, with a cost of around $10 to $40 per unit, depending on size. Puracol® is considered the most cost-effective option of common xenograft skin substitutes available for use.[16]

The use of bovine-derived collagen wound dressing (BCWD, ie, Puracol®) has been investigated for wounds after Mohs micrographic surgery of the scalp and the lower extremities.[16,17] It was found to reduce the time to granulation of wounds with exposed bone, reduce the time to complete reepithelialization, diminish wound drainage, and decrease pain. Additionally, there is anecdotally reported evidence of improved cosmetic appearance after BCWD use compared to second-intention healing alone for scalp wounds.[16] In our experience, BCWD can be successfully used in any anatomic region with all of these same benefits. Here, we present a single-center case series experience with descriptive statistics of the use of BCWD in nasal defects after Mohs micrographic surgery.

MATERIALS AND METHODS

This study was approved by the institutional review board of Ascension St. Vincent Indianapolis. A retrospective review was performed at our single-site private practice of all applications of BCWD on Mohs micrographic surgery defects of the nose, performed between January 2022 and June 2023. Exclusion criteria were if any other forms of wound closures were additionally performed, such as a delayed full-thickness skin graft or flap or BCWD used in combination with a primary closure.

The process of applying BCWD at our practice is the following. After surgical clearance of skin cancer of the nose, BCWD were sutured to the existing epithelial wound edge and wound bed with 4-0 or 5-0 chromic gut. A non-bolstering pressure bandage was applied for 24 to 48 hours, and then patients continued daily wound care with petroleum jelly (Vaseline) and a non-stick gauze pad. Patients were instructed to shower with a bandage in place to avoid direct water pressure disturbing the graft. Patients returned for follow-up visits approximately every 4 weeks. Incidence of postoperative bleeding, drainage, pain, and surgical site infection were documented during these encounters. The date of complete re-epithelialization was recorded as either the patient-reported date or, if the patient could not recall, as the date of the follow-up visit upon confirmation of complete healing by one of the authors (JD, ES, and CWH). In addition, on follow-up visits where complete healing is noted, one of the authors (JD and ES) rated the cosmetic appearance of the final scar on a visual 3-point scale rating of "poor", "acceptable", or "outstanding". "Poor" outcomes were defined by significant atrophy, hypertrophy, notching, or other features requiring intralesional injection, surgical revision, or resurfacing. "Acceptable" outcomes were defined as minimal to slight atrophy or hypertrophy, not requiring further intervention. "Outstanding" outcomes were defined as a nearly imperceptible scar.

The medical records for all subjects were reviewed. Demographic data, medical history, and surgical data, including tumor type, location on the nose, number of Mohs stages, and depth of wound were coalesced. The primary outcome analyzed was time to re-epithelialization, which was compared to previously published historical controls of time to re-epithelialization of second intention healing of the nose.

RESULTS

Thirty-nine patients with 39 tumors were included in this study. The surgeries and subsequent follow ups ranged from January 2021 to June 2023. All tumors were treated with Mohs micrographic surgery and a single application of BCWD. No other reconstruction method was performed. Patient demographics are outlined in Table 1. The mean age at the time of surgery was 74 years, with a slight majority of patients of male gender (54%). Smoking, use of anticoagulants, and history of diabetes were also recorded. No patients were on immunosuppressive medication.

Procedural characteristics of the tumor type, location on the nose, and depth of tumor extirpation are described in Table 2. Basal cell carcinoma was the majority of the cases (77%), followed by squamous cell carcinoma (18%) and melanoma (5%). Location on the nose was categorized by nasal sidewall (10%), nasal root (3%), nasal dorsum (31%), nasal tip (33%), and nasal ala (23%). The majority of the wounds had depth to the fat (90%).

TABLE 1.

Patient Demographics	
Age in years, mean (SD)	74 (13.3)
Male gender, n (%)	21 (54)
Smoking, n (%)	
Yes	2 (5)
No	37 (95)
Anticoagulants, n (%)	
Yes	19 (49)
No	20 (51)
Diabetes, n (%)	
Yes	3 (8)
No	36 (92)

TABLE 2.

Procedure Characteristics	
Cancer type, n (%)	
Basal cell carcinoma	30 (77)
Squamous cell carcinoma	7 (18)
Melanoma	2 (5)
Nose Location, n (%)	
Sidewall	4 (10)
Root	1 (3)
Dorsum	12 (31)
Tip	13 (33)
Ala	9 (23)
Depth of wound, n (%)	
Fat	35 (90)
Muscle	2 (5)
Perichondrium	1 (2.5)
Cartilage	1 (2.5)

TABLE 3.

Outcomes	
Length of follow-up in days, mean (range)	50 (27-221)
Time to Re-epithelialization in days, mean (range)	33 (11-60)
Post-excision wound area in cm^2, mean (range)	1.7 (0.48-7.5)
Post-epithelialization wound area in cm^2, mean (range)	0.7 (0.12-3.75)
% wound contraction after re-epithelialization, mean	54 (-210-92)
Complications, n (%)	
Bleeding	10 (25.6)
Drainage	19 (48.7)
Pain	8 (20.5)
Infection	0 (0)
Physician rating of cosmetic outcome	
Poor	9 (23)
Acceptable	14 (35.9)
Outstanding	16 (41)

Table 3 depicts a descriptive analysis of outcomes. All 39 patients were followed until at least the time of reepithelialization, and 23 patients were followed after re-epithelialization, between one week and several months after healing. The mean follow-up time was 50 days. The mean post-excision wound surface area was 1.7 cm^2, and the mean time to re-epithelialization was 33 days. In terms of the rate of healing, this equates to 19.4 days per cm^2 of defect size (33 days/1.7 cm^2).

Mean post-excision and post-epithelialization wound areas were 1.7 cm^2 and 0.7 cm^2 respectively, demonstrating a mean wound contraction of 54%. Rates of complications were overall low, with 25.6% experiencing bleeding, 48.7% experiencing drainage, and 20.5% experiencing pain at the surgical site. Antibiotic prophylaxis for 7 days was used in all cases. No incidences of infection requiring the need for further antibiotics during the course of healing occurred. The majority of healed wounds had "outstanding" (41%) or "acceptable" (35.9%) cosmetic outcomes, with 23% of wounds rated as "poor".

DISCUSSION

Skin substitutes have gained increased interest in recent years as useful tools to aid in second-intention healing for wounds after skin cancer excision. While the successful and effective use of BCWD (Puracol®) has already been reported for wounds of the scalp and lower extremity, its application for nasal defects has not been investigated until now.[16,17]

The predominant benefit seen with the use of BCWD in established studies is an increased rate of healing compared to second-intention healing. In a case series of 11 scalp wounds with calvarium exposed healed with BCWD, wounds reepithelialized 70% faster compared to historical controls of scalp wounds healed by second intention healing alone.[16] This is similar to our experience. The rate of healing of our case series demonstrated a re-epithelialization rate of 19.4 days per cm^2 of defect size. As a historical comparison, 2 studies have published a case series of nasal defects healed with second intention healing.[18,19] Yeh et al featured 6 patients with nasal defects with an average defect size of 0.77 cm^2 and an average time to reepithelialization of 25.7 days, equating to 33.4 days per cm^2 of defect size.[18] Jin et al performed a separate case series of 10 patients with nasal defects with an average defect size of 0.39 cm^2 and an average time to re-epithelialization of 17.7 days, equating to 45.7 days per cm^2 of defect size.[19] Therefore, in our case series, BCWD increased the rate of healing by 42 to 58% compared to second-intention healing alone.

In our experience, BCWD may also enhance cosmetic outcomes of nasal defects over second-intention healing. An atrophic or "divoted" contour is of predominant cosmetic concern when choosing second-intention healing to heal a post-Mohs defect of the nose. The addition of BCWD to the nasal wound defects can result in a more favorable and "filled" contour. Of the 39 surgical defects, 30 (77%) had an outstanding or acceptable cosmetic result (Figure 1). The 9 surgical defects rated as "poor" were all of size 1 cm^2 or larger, including one patient with a 3 x 2.5 cm defect of the nasal ala to the depth of cartilage who refused a flap or graft. Three of the defects had predictable

FIGURE 1. 1.0 x 1.0 cm defect of the nasal dorsum treated with a single application of BCWD. Left photo is immediately after tumor extirpation. Middle photo with BCWD sutured in place with chromic gut. Right photo on follow-up at month 4. This is an example of a typical cosmetic outcome of a scar rated as "outstanding" with minimal to no contour deformity, good light reflection, and minimal to no residual dyspigmentation or erythema.

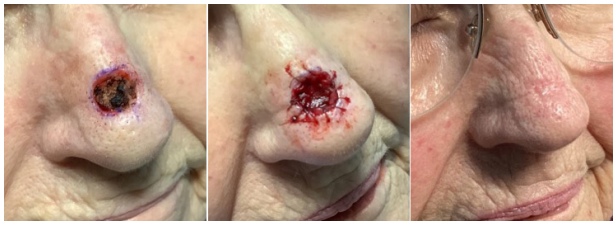
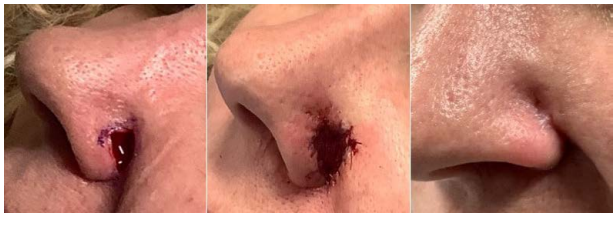


FIGURE 2. 1.1 x 1.1 cm defect of the left nasal ala treated with a single application of BCWD. Left photo is immediately after tumor extirpation. Middle photo with BCWD sutured in place with chromic gut. Right photo demonstrates the scar at follow-up 3.5 months after surgery. The scar was rated as a "poor" cosmetic outcome due to the presence of webbing.



anatomic region-associated complications, such as webbing of the medial canthus and nasolabial fold and alar notching (Figure 2). The other defects all exhibited atrophy or hypertrophy that resolved to good patient satisfaction after laser resurfacing, dermabrasion, or intralesional steroid injections.

Patients should be counseled to expect shrinkage of the wound defect due to inherent wound contraction. Nasal defects healed by the second intention demonstrate wound contraction by 59 to 79%.[20] Our case series showed a similar mean wound contraction of 54%, suggesting that BCWD does not affect this natural beneficial process.

CONCLUSION

BCWD is an effective and safe skin substitute that facilitates second-intention healing for excisional wounds of the nose through faster healing time, excellent cosmetic outcome, and minimal pain, bleeding, and drainage.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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BRIEF COMMUNICATION

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Delayed Inflammatory Reactions to Hyaluronic Acid Fillers: A Case Series of Novel Associations

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ABSTRACT

Background: Delayed reactions to hyaluronic acid (HA) fillers have been reported following various immunologic and infectious triggers.
Aim: Herein, we describe cases of delayed immunologic reactions (DIRs) following HA-soft tissue augmentation fillers precipitated by triggers not previously described in the literature.
Patients: Case 1 describes a 57-year-old female with DIR to HA-filler following a motor vehicle accident in the marionette lines and nasolabial folds. Case 2 is a 54-year-old female who had a filler-related DIR following an episode of contact dermatitis shortly after laser resurfacing. Finally, in Case 3, we diagnosed a 54-year-old female with DIR to HA-filler on the hands following prolonged gardening without gloves.
Conclusion: DIRs are an important filler-related complication. Practitioners need to be aware of the variable clinical presentations and a wide array of triggers. Given that these may not always be preventable, it is important for patients to understand the risk of DIRs, albeit low.

J Drugs Dermatol. 2025;24(1):101-103. doi:10.36849/JDD.8468

INTRODUCTION

Hyaluronic acid (HA) fillers have become increasingly popular in non-surgical rejuvenation procedures. They are easy to administer and help in addressing various cosmetic concerns, making them a popular option among practitioners. Moreover, their reversible nature and excellent safety profile have led to increased use.

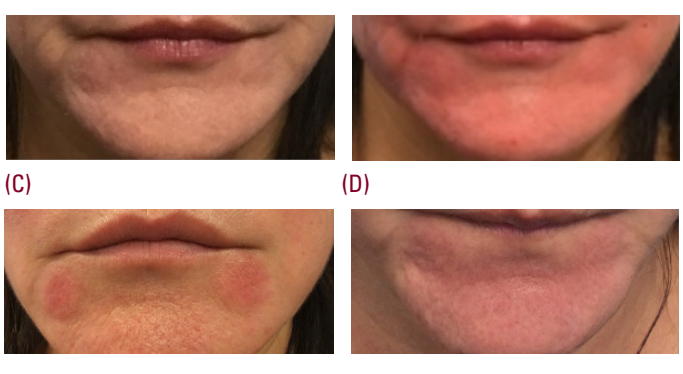
Immune reactions are uncommon but well-described following HA-fillers and can be either immediate or delayed. Delayed immune reactions (DIRs) may present as nodules, edema, and/or erythema. Various triggers for DIRs have been described. Herein, we add to the literature three cases of DIRs to HA-fillers: one triggered by a motor vehicle accident, one following significant plant exposure while gardening without gloves, and another following an episode of contact dermatitis after laser resurfacing.

Case 1

A 57-year-old woman with phototype-IV skin presented to our clinic on May 2nd, 2018, concerned about volume loss and facial aging of the lower third of the face. She had deep wrinkles in the marionette lines and oral commissures, with mildly prominent nasolabial folds. Her medical history included osteoarthritis and herpes simplex. She had no drug allergies or history of autoimmune disease.

Based on her cosmetic goals, 1 mL of Restylane® Refyne was injected in the nasolabial folds and marionette area, and 1 mL of Restylane® Defyne was injected in the secondary smile lines following three rounds of disinfecting with alcohol and chlorhexidine-based solution. The injection of these HA fillers was performed in a deep subdermal plane. Areas of filler placement were subsequently molded and massaged to minimize clumps. No visible or palpable nodules were present upon discharge (Figure 1A and 1B).

FIGURE 1. (A) Photograph prior to filler. (B) Immediately following filler in the marionette lines, nasolabial folds, and smile lines. (C) Erythema and swelling at the marionette lines 3 months following a motor vehicle accident. (D) Improvement of erythema and swelling following hyaluronidase.



Two weeks later, the patient was involved in a motor vehicle accident, sustaining multiple injuries, including concussion and abrasions over the head, neck, trunk, and extremities. Notably, she did not have an infection and was not treated with antibiotics. Extensive exposure history otherwise revealed no recent dental procedures, vaccines, or infections preceding the flare.

Photos immediately following the accident while in urgent care revealed no erythema or swelling of the face. However, in the weeks that followed, she developed increasing swelling at the sites of prior filler injections. On follow-up 8 weeks after the accident, she had persistent redness and swelling over the marionette area and nasolabial folds (Figure 1C).

DIR to HA filler was diagnosed, which is suspected to have been triggered by physiologic stress and skin barrier compromise from minor abrasions following a motor vehicle accident. The patient opted for filler dissolution, and 50 units of Hylenex® (hyaluronidase) was administered to each side (Figure 1D).

Case 2

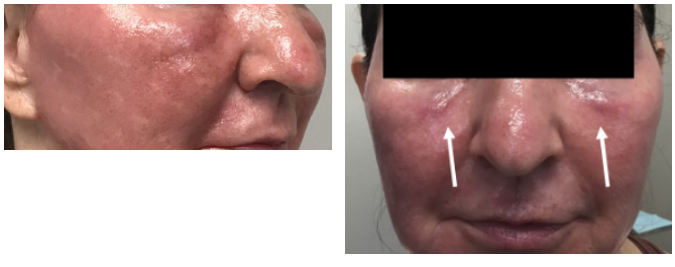
A 54-year-old woman with phototype-II skin presented to our clinic on August 28th, 2023, for recommendations to improve texture and dyschromia on the chest, as well as fine etched lines and sebaceous skin on the face. Several months prior to consultation with us, she had filler injected infraorbitally as well as in the cheeks at another facility (Juvéderm Voluma® in both areas). She had no known drug allergies, and her past medical history was otherwise unremarkable.

At our clinic, she underwent a session of a fractional ablative erbium laser for the face as well as a hybrid ablative and non-ablative fractional laser for the chest and neck. Following treatment, platelet-rich plasma was applied over the full face in a sterile manner. Post treatment instructions were given: regular use of a post-procedure cleanser (Don't Be So Sensitive®), dilute hypochlorous acid (HypoCyn®), and regular use of post-treatment petrolatum, in addition to maintaining good facial hygiene.

On follow up 2 days later, she was noted to have increasing redness and itching in the treated areas. On examination, there was uniform, well-demarcated erythema over the face, with no bumps, pustules, or drainage (Figure 2A). The cleanser was discontinued and switched to a Vanicream® cleanser, and she was started on doxycycline empirically. The dilute hypochlorous acid and white petrolatum were continued. The following day, she reported that her symptoms had significantly improved up until she re-applied the HypoCyn® product. She was advised to discontinue this hypochlorous acid antimicrobial product, and her symptoms and redness resolved over the following two days. Bacterial cultures taken prior to initiation of antibiotics were negative.

FIGURE 2. (A) Sharply-demarcated erythema and swelling on the face at the site. (B) Swelling and erythema at the site of prior infraorbital filler placement following laser treatment and suspected contact dermatitis.

(A) (B)



Given the significant itching, sharp demarcation of erythema, temporal association with topical product use, and rapid resolution following discontinuation, we suspect that the patient had an irritant contact dermatitis secondary to the hypochlorous acid product, likely provoked in the setting of a compromised skin barrier following laser therapy.

Notably, at the day 2 post-laser follow-up visit, the patient had pronounced erythema and swelling of the infraorbital area at the sites of the previous filler injection. Although the redness from the suspected contact dermatitis resolved within a few days, the infraorbital erythema and swelling persisted for weeks afterward (Figure 2B). We suspect the patient had a filler-related DIR following an episode of contact dermatitis after laser resurfacing.

Case 3

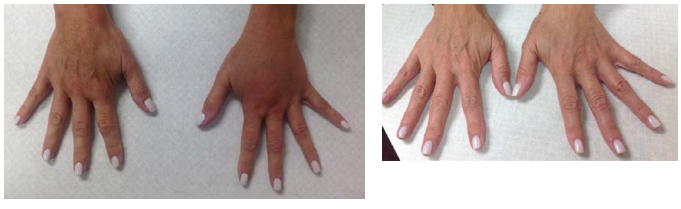
A 54-year-old woman with phototype-III skin presented to our clinic in March 2016 for treatment of aging of the dorsal hands. On examination, she had mild volume loss and signs of photoaging on the dorsal hands bilaterally with slightly visible veins. She had no medical conditions and no known drug allergies or autoimmune diseases.

As part of a clinical trial, she had Restylane® Lyft filler injected in the left dorsal hand, which was well tolerated. Three months later, she presented to our clinic for follow up for swelling, itching, and soreness of the left hand that had progressed over two weeks. Exposure history was reviewed in detail, revealing no recent dental procedures, vaccines, or infections. After detailed discussions with her and her husband, it was elucidated that she had been gardening without gloves 2 days prior to the onset of the swelling.

On examination, exhibited non-pitting edema over the left dorsal hand at the filler injection sites, without any erythema, tenderness, or fluctuance (Figure 3A). She had no fevers or chills and felt otherwise well. Notably, she had HA filler to the eyelids and lips six months prior, which were also now swollen.

FIGURE 3. (A) Erythema and non-pitting edema of the left dorsal hand three months following HA-filler (no filler was injected to the right hand). (B) Resolution of DIR following treatment with hyaluronidase and prednisone.

(A) (B)



We diagnosed DIR to HA filler triggered by transient bacteremia due to minor abrasions on the hands sustained while gardening without gloves. After conservative management with a trial of non-sedating antihistamines and 2 courses of antibiotics (clarithromycin and moxifloxacin), the swelling persisted. As such, 150 units of Hylenex® were injected into the left dorsal hand, with repeat injection two days later. A 2-week prednisone taper starting at 40 mg was also given, resulting in significant improvement (Figure 3B).

DISCUSSION

DIRs are an uncommon complication that occurs following soft tissue augmentation, including with HA dermal fillers.[1] They are unpredictable and may occur in both previously injected and first-time patients.[2] Although definitions vary, an expert panel[3] agreed that DIRs occur at least two weeks following filler administration, after a quiescent state prior to flare-up. Reactions may manifest as erythema, edema (usually solid, non-pitting), nodules, and/or induration. Although DIRs are categorized as one entity, they likely represent a spectrum with infectious and immune-related pathogenesis being most likely.

Different triggers have been associated with DIRs, many of which are linked to injector-related circumstances such as inadequate skin preparation, large filler volume, repeated treatments, intramuscular implantation, and improper technique.[4,5] However, product-related factors have also been implicated. Specifically, HA fillers, composed of sodium hyaluronate cross-linked with 1,4-butanediol diglycidyl ether, vary in their cross-linking process depending on the manufacturer. It is hypothesized that larger molecules that are no longer recognized by the body as HA may lead to foreign-body reactions. Additionally, impurities or bacterial contamination from the cross-linking process may precipitate DIRs.[2]

The specific immunologic mechanisms by which DIRs occur are not entirely understood. One hypothesis suggests a cell-mediated hypersensitivity reaction, whereby low-molecular-weight HAs and by-products become immunogenic, leading to a delayed-type hypersensitivity reaction and downstream cytokine cascade. Beleznay et al[4] suggest that these pro-inflammatory HA fragments may be released following triggers that lead to a systemic inflammatory response. Infectious, biofilm-related, and other foreign-body reactions are also considered etiologic possibilities.

Regardless of the mechanisms, various triggers of DIRs have been described, including infections (especially respiratory), immunologic phenomena (vaccines), and trauma (dental procedures).[3,6,7] To the authors' knowledge, no case of filler reactivation has been reported following motor vehicle accidents, gardening, or contact dermatitis after laser resurfacing.

The management of DIRs depends on various factors, including the severity of clinical manifestations. For example, diffuse erythema and non-pitting edema at filler sites would be managed differently than small, isolated nodules. An expert panel describes a stepwise approach[3] to managing DIRs, which includes watchful waiting, systemic corticosteroids, incision and drainage of abscesses, antimicrobials, hyaluronidase, as well as intralesional corticosteroids and/or 5-FU.

CONCLUSION

The popularity of HA fillers is increasing, and as such, injectors need to be equipped to manage and counsel patients on complications such as DIRs. We presented three cases of patients who developed DIRs to HA fillers following different triggers: motor vehicle accident, gardening without gloves, and suspected contact dermatitis following laser resurfacing. Overall, the exact mechanism by which DIRs occur is not fully clear. However, various systemic inflammatory insults, physiologic stressors, or skin barrier compromise may trigger these reactions. Given that these may not always be preventable, it is important for patients to understand the risk of DIRs occurring, albeit small.

DISCLOSURES

The authors have no conflicts of interest to declare.

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NEWS, VIEWS, AND REVIEWS

Vessel-Targeting Therapies for the Management of Rosacea: A Review of Current Evidence

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INTRODUCTION

Rosacea, a condition defined by persistent erythema, may also present with flushing, telangiectasias, edema, enlarged facial blood vessels, and/or vascular nets.[1,2,3] The pathophysiology of rosacea is believed to be a culmination of neurovascular dysregulation, altered immune detection and response, and long-term changes to the skin's superficial vasculature.[3] Alterations in the vasculature result from increased angiogenesis, disruptions in cutaneous vascular homeostasis, and endothelial cell damage from inflammatory byproducts.[2] These aberrant processes culminate in progressive vascular changes, beginning with increased blood flow to affected skin, followed by persistent vasodilation and proliferation, and ultimately permanent vascular changes.[3]

Rosacea management is multimodal, employing treatments that modulate inflammation and vascular function. Vessel-targeting therapies, including alpha (α) agonists, beta (β) blockers, and laser and light-based therapies, are mainstays in rosacea treatment. Modulation of α and β receptors capitalizes on the sympathetic nervous system's (SNS) role as the primary regulator of the cutaneous vasculature, while light and laser therapies target vasculature and related inflammation.[2,3] This review highlights current evidence supporting the use of various vessel-targeting therapies for rosacea.

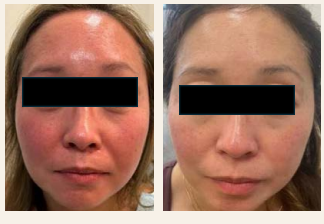
Alpha Agonists

As rosacea's persistent facial erythema (PFE) is secondary to SNS-driven enlargement of superficial cutaneous vasculature, α-agonists are supported for use by level B evidence and recommendations published by the American Acne & Rosacea Society (AARS).[1,2] α-agonists' efficacy results from targeting α-adrenergic receptors in the smooth muscle layer of superficial cutaneous blood vessels.

Oxymetazoline hydrochloride 1% cream is an α1-adrenergic receptor agonist FDA-approved for treating PFE. Clinical studies have shown once daily oxymetazoline to be effective, safe, and tolerable in improving moderate-to-severe PFE. Oxymetazoline's effects typically begin within 1 to 3 hours, lasting up to 12 hours. Phase III studies showed a 2.2% rate of worsening or rebound erythema (similar to 1.1% in controls), and 23.4% of oxymetazoline users reported increased itching. Brimonidine tartrate 0.33% gel, an α2-adrenergic receptor agonist, is FDA-approved for transient and PFE. Though generally safe, up to 8% of patients may experience transient worsening or rebound erythema.[1,2,4] Proposed differences in the anatomic distribution, density, and mechanisms of α1 versus α2 receptors may explain the prevalence of paradoxical erythema with brimonidine.[5] Regardless, the unintended erythema associated with brimonidine has made oxymetazoline the favored topical α-agonist.

The oral α-2 adrenergic agonist, clonidine, has been shown to reduce flushing and blushing without lowering blood pressure at doses of 0.05 mg twice daily (Figure 1). While some patients respond well to clonidine, no clinical markers have been identified to delineate which patients will benefit, making a trial course of clonidine practical.[6]

Figure 1. A patient prior to treatment (left) and two months into treatment with clonidine 0.5 mg twice daily (right).



Beta Blockers

Studies of vessel reactivity have shown that β-adrenergic receptors, specifically β-1 receptors, are the most highly expressed adrenergic receptors in cutaneous arteries and arterioles, functionally facilitating vasodilation.[7] β-blockers, a class of vasoconstrictors, have been used to treat flushing (supported by level B evidence) and erythema in rosacea.[1]

In a systematic review of nine studies investigating oral β-blockers for mostly treatment-refractory rosacea, the nonselective β-blockers carvedilol (6.25 to 37.5 mg daily) and propranolol (30 to 120 mg daily) effectively reduced erythema and flushing unresponsive to conventional therapy, while nadolol showed no significant improvement. Rosacea symptoms improved quickly with treatment, and carvedilol was better tolerated than propranolol despite risks like bradycardia, hypotension, and contraindications, including exacerbation of asthma and psoriasis.[8]

Two split-face studies of the topical β-blocker, timolol, have demonstrated improvements in erythema, burning, and warmth after use. However, some results were confounded or limited by short-term use. Timolol is considered safe, with mild side effects, including transient skin sensitivity and erythema.[9,10]

Light and Laser Treatments

Laser treatments have exhibited efficacy in addressing refractory background erythema and prominent linear blood vessels in rosacea, while photodynamic therapy (PDT) has been postulated to modulate inflammation. The AARS recommends laser therapies (pulsed dye laser (PDL), intense pulsed light (IPL), and potassium titanyl phosphate (KTP)) for use in PFE, supported by level B evidence.[1,2,11]

Both IPL and PDL effectively reduce erythema, flushing, and telangiectasias in patients with rosacea, with studies showing their comparable efficacy. IPL penetrates deeper tissues and achieves up to 75–100% clearance of erythema and telangiectasias with minimal side effects. PDL targets superficial vessels and thicker/denser telangiectasias with significant erythema reduction but may cause purpura and dyspigmentation. Successful treatment of cutaneous vessels has also been observed with KTP, neodymium:yttrium-aluminum-garnet, and diode lasers.[1,2]

Some findings suggest the efficacy of combining lasers with topical α-agonists; while lasers address diffuse facial erythema and telangiectasias, topical α-agonists can minimize post-treatment erythema.[1] Mouse studies suggest enhanced vascular shutdown with PDL and oxymetazoline combined, and a retrospective study found significant improvements in rosacea severity and telangiectasia clearance with daily oxymetazoline and PDL treatment(s).[4]

The efficacy of PDT for rosacea was demonstrated in a systematic review of nine studies in which PDT treatments achieved satisfactory clinical responses with mild, self-resolving side effects.[11]

Additional Vessel-Targeting Therapies

Off-label botulinum toxin (BTX) injections can effectively reduce flushing, supported by level B evidence, and diminish erythema. A randomized control trial of 15 patients showed significant improvement in erythema with BTX injections, with consistently positive results across varying dosages and treatment frequencies.[1,2]

A recent study showed the efficacy of paroxetine (selective serotonin reuptake inhibitor) 25 mg daily in improving refractory, moderate-to-severe erythema, flushing, and burning.[12] Small, older studies showed rilmenidine (central hypotensive drug) 1 mg daily was ineffective at reducing erythema and flushing, while ondansetron (serotonin agonist) 12 to 16 mg daily improved PFE and naloxone (opioid antagonist; unspecified dose) reduced alcohol-induced flushing, but with significant side effects. Phentolamine (α2-agonist), administered transcutaneously, paradoxically increased facial blood flow during exercise.[8]

CONCLUSION

Among vessel-targeting therapies, topical α-blockers (oxymetazoline, brimonidine) and laser treatments have the highest evidence for treatment of PFE, while low-dose β-blockers (propranolol, carvedilol) and intradermal BTX are superior for the treatment of flushing.[1] Vessel-targeting therapies are core components of rosacea treatment regimens and can be leveraged to address patient-specific phenotypes and concerns.

DISCLOSURE

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