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Glaucoma: Under Pressure to Treat

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Executive Summary

Glaucoma is a term for a heterogeneous group of diseases that all have one feature in common—optic nerve damage that leads to irreversible vision loss and eventual blindness without treatment.[1] For the first time in decades, there has been a major paradigm shift in the way that glaucoma is diagnosed and treated, and commensurate growth in research and development for this indication. This paper aims to give an overview of glaucoma, including disease impact, pathophysiology, diagnosis, and treatment.

The major focus here will be on new and emerging treatment modalities for open-angle glaucoma that allow physicians to expand their armamentarium and patients to renew their hope. Glaucoma is no exception to the movement towards practicing evidence-based medicine through a patient-centered lens.[2] To that end, efficient and meaningful clinical trials are more critical than ever to reduce disease burden for patients and treatment burden for physicians.

Introduction

Disease Impact

Glaucoma is a leading cause of blindness worldwide and is the leading cause of irreversible blindness. According to the World Health Organization (WHO), over 60 million people are affected with glaucoma, and over 4.5 million people are blinded as a result of the disease.[3] Ten percent of those who are blind from glaucoma are affected bilaterally.[4] Eighty percent of glaucoma in the United States is of the open-angle type, however, vision loss occurs more often in angle-closure glaucoma.[5] The WHO classifies glaucoma as a priority eye disease, alongside age-related macular degeneration, cataract, and refractive error[3].

Because glaucoma affects the peripheral vision before central vision, it often shows no symptoms. This is unlike other leading causes of blindness, such as cataract, refractive error, or macular degeneration, that cause a symptomatic decrease in the central vision that is noticed by the patient and prompts medical attention. Less than half of people affected with glaucoma know that they have it and are at risk for progression.[6,7]

Pathophysiology

Glaucoma causes progressive damage to the optic nerve fiber loss via degeneration of the retinal ganglion cells. This leads to the finding of cupping upon physical exam, where the central portion of the optic nerve becomes excavated. Functionally, there is loss of peripheral vision that, without treatment, will eventually encroach on the central axis.[8]

Glaucoma can be classified in terms of anatomy, as well as underlying cause. Open-angle glaucoma refers to a condition where the anatomy of the drainage system appears normal, however, there is an imbalance between aqueous humor production and aqueous outflow. Angle-closure glaucoma is a result of an abnormally narrow and eventually closed anatomical drainage system. Both open-angle and angle-closure glaucoma can be primary diseases, or secondary to another process, such as trauma, inflammation, tumor, or medications such as corticosteroids.

The common denominator, and the physiologic sign that is treated in glaucoma, is intraocular pressure (IOP). Other known risk factors for development of glaucoma include being of older age, Black race, having a family history of glaucoma, and use of topical or systemic corticosteroids.[9]

The present discussion will focus on open-angle glaucoma diagnosis and treatment modalities.

Diagnosis

Because glaucoma is often asymptomatic, diagnosis is largely based on screening during routine eye examinations or examinations for unrelated eye complaints. Elevated intraocular pressure can prompt further evaluation, including increased cup-to-disc ratio, cup-to-disc ratio asymmetry between the two eyes, hemorrhage at the optic disc, or signs of secondary glaucoma such as pseudo-exfoliation or pigment dispersion.[10] Optic nerve head photographs can also be obtained to visualize and track disease progression.[11] Gonioscopy, or visualization of the angle via a special lens, can be performed to properly classify the disease, and the central corneal thickness is often measured.

Automatic visual field testing is routinely performed on glaucoma suspect patients to identify any defects in the peripheral vision, and serial visual field testing is a part of monitoring for disease progression in individuals being treated for glaucoma. However, by the time there is objective visual field loss on these studies, 30-50% of retinal ganglion cells may be lost already.[12] In addition, visual field testing and interpretation of photographs of the optic nerve are subjective data.

Imaging assessment of the optic nerve and retinal nerve fiber layer (RNFL) is now standard of care in order to provide quantitative and objective data. These modalities include optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy, and scanning laser polarimetry.[13] These modalities have evolved to offer granular detail of the anatomy and structural relationships of the tissues involved in glaucoma.

Current Treatment

Reduction of intraocular pressure is the goal of treatment in all forms of glaucoma. The goal of treatment is to halt disease progression—not to restore sight—and to allow maximal quality of life in the context of visual decline.[14] Several multicenter clinical trials, such as the Ocular Hypertension Treatment Study (OHTS), the Early Manifest Glaucoma Trial Group, and the Advanced Glaucoma Intervention Study (AGIS), have shown the benefits of reducing eye pressure to prevent glaucoma or slow progression.[15-17]

Target IOP is often defined initially as reduction from baseline by 20-50% , depending on the severity of the disease. However, these targets can vary between individuals and in each eye, depending on the extent of baseline damage, risk factors for progression, life expectancy, lifestyle considerations, and potential toxicity from treatment. The target IOP is ideally achieved with the fewest interventions and the least side effects. Often, management of glaucoma requires multiple modalities—staged and sometimes simultaneous—and close follow-up with the glaucoma specialist to detect treatment failure and progression despite target pressure.

Topical Medications

Until about two decades ago, there were four classes of topical eye drops to treat glaucoma. These include beta-adrenergic blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agents. Effectively managing glaucoma medically often requires multiple topical agents or the use of combination ophthalmic eye drops. Combinations currently on the market include Combigan (Allergan), an alpha-agonist/beta-blocker, Cosopt (Merck), a carbonic anhydrase inhibitor and beta-blocker, and Simbrinza, a carbonic anhydrase inhibitor plus alpha-agonist.[18]

The prostaglandin analogues emerged as a fifth class in 1996 with the FDA approval of latanoprost, and up until very recently have held their place as first-line therapy due to their efficacy, once-a-day dosing and local only side-effect profile. They function by reducing outflow resistance to aqueous via the uveoscleral pathway. They stand out from the other classes in that they have no systemic side-effects, only causing local conjunctival redness, eyelash growth, and iris and skin darkening in some cases. They are dosed nightly instead of two or three times a day, and therefore promise better compliance.[19]

Since 2017, the FDA has approved three new topical agents for the treatment of open-angle glaucoma – Vyzulta (Bausch&Lomb), Rhopressa (Aerie) and a combination agent, Rocklatan (Aerie).[20] These new approvals come after more than two decades of quiescence in drug development for glaucoma.

Latanoprostene bunod (Vyzulta) is a novel prostaglandin analogue that is nitric oxide donating. Once it is administered onto the ocular surface, it is metabolized into latanoprost (a conventional prostaglandin analogue) and butanediol mononitrate, a nitric oxide donating moiety. Both compounds have been shown to reduce IOP, the former through the uveoscleral

pathway, and the latter through relaxation of the trabecular meshwork. This agent has been demonstrated to be non-inferior to standard of care (timolol maleate) in multiple clinical trials, including the LUNAR study and the APOLLO study.[21-22]

Netarsudil (Rhopressa) is an entirely new class of ocular anti-hypertensive, a rho-kinase inhibitor (ROCK) and norepinephrine transporter (NET) inhibitor. It has been shown in pre-clinical models to work via three mechanisms–increases trabecular outflow, decreases aqueous production, and decreases episcleral venous pressure. In the ROCKET Phase III trial, this topical therapy has been shown to consistently reduce IOP and was well-tolerated.[23]

Rocklatan is a combination of netarsudil and latanoprost that was FDA approved in March of 2019.

Laser Trabeculoplasty

Laser treatment of the trabecular meshwork offers an alternate treatment option for patients who are non-compliant with topical medications for various reasons, including cost, memory issues, arthritis, or intolerable side effects. Often, laser treatment is used as a first line therapy. Recently, the National Institute of Health (NIH) funded a multicenter, randomized, controlled trial comparing medication to selective laser trabeculoplasty, which supports this change in the treatment paradigm.[24]

Laser treatment lowers IOP by improving trabecular aqueous humor outflow. It was traditionally performed using argon laser (ALT); however, increased use of this treatment option was in response to introduction of selective laser trabeculoplasty (SLT), using a Nd:YAG laser. SLT offers selective absorption by pigmented cells in the trabecular meshwork, creates less thermal damage, and can be repeated multiple times, with comparable efficacy to argon treatment.[25]

Incisional Surgical

Both trabeculectomy and aqueous shunt placement are ab-externo surgical procedures often reserved for glaucoma that progresses despite a combination of multiple medications and/or laser treatment. Creating these surgical conduits allows aqueous to bypass the physiological outflow mechanisms by creating a path into the subconjunctival space. Aqueous shunt placement is often reserved for treatment after failure of trabeculectomy.

These surgical interventions often require the adjunctive use ofanti-fibrotic agents such as mitomycin-C (MMC) or 5-fluorouracil either intraoperatively or in the post-operative period to prevent failure. They also require intensive post-operative corticosteroid treatment, and close follow-up. With the introduction of laser and micro-invasive glaucoma surgery (MIGS), these procedures are most often reserved for severe cases of open-angle glaucoma. Success rates range in various studies from 31 to 88% [26], and success is difficult to define as often control of glaucoma with surgery results in other complications that reduce central vision, including hypotony maculopathy and infection.

The Ex-PRESS shunt (Alcon Laboratories, Fort Worth, TX) is a device that has been found to be of comparable efficacy to trabeculectomy with a similar mechanism, but obviates the need for sclerostomy and iridectomy, thus making it a less invasive surgery. However, there is a higher cost due to device implantation, and some evidence of increased early hypotony.[27]

Glaucoma surgery can be and is often combined with cataract surgery, as the demographics for both diseases heavily intersect. There is some evidence that in certain cases, cataract surgery alone may be enough to lower IOP, and can be considered an option for surgical glaucoma treatment in patients who require only modest pressure reduction.[28]

Other surgeries less often used include deep sclerectomy, viscocanalostomy, canaloplasty, and cyclodestructive surgery, and gonioscopy assisted transluminal trabeculotomy.

Micro-invasive Glaucoma Surgery (MIGS)

MIGS, or micro-invasive glaucoma surgery, is a new class of procedures that has emerged over the past ten years and is ever evolving in terms of device approval and modification. The number of devices continues to increase with more refined characteristics and various theoretical mechanisms.

Saheb and Ahmed provide a useful definition of MIGS as having the following five characteristics:

1. Ab externo approach through cornea and not conjunctiva
2. Minimal trauma to ocular tissue
3. IOP lowering efficacy
4. High safety profile compared to other glaucoma surgery
5. Rapid recovery with minimal impact on quality of life.[29]

In a workshop of the American Glaucoma Society and the FDA, MIGS was defined as implantation of a surgical device to lower IOP with little or no scleral dissection.[30]

MIGS procedures are done under the microscope through incisions and with implants that are measured in millimeters. Like laser trabeculoplasty, the aim is to mitigate the complications of filtration surgery while still lowering IOP to target. MIGS theoretically offers a way to do this while sparing the conjunctival tissue for future surgery, as glaucoma is a chronic, progressive disease often requiring stepwise treatment over a lifetime. MIGS is commonly performed alongside cataract surgery.

The iStent (Glaukos, Laguna Hills, CA), the iStent Inject (Glaukos, Laguna Hills, CA) and the Hydrus (Ivantis, Irvine, CA) are three devices that modulate the trabecular outflow pathway. They are all surgical injected into Schlemm's canal to this effect.

The iStent Supra (Glaukos, Laguna Hills, CA) and the Cypass (Alcon, Fort Worth, TX) are devices that target suprachoroidal outflow pathway. Cypass was voluntarily taken off the market after long-term safety data indicated significant increase in corneal endothelial cell loss.

The Xen Gel Stent (Allergan, Dublin, Ireland) implant allows increased outflow from the anterior chamber into the subconjunctival space.[31]

Emerging Treatment

Novel Drug Delivery

It is a prolific period in the research and development of glaucoma therapeutic agents and devices, with 199 Phase III studies registered on Clinical Trials.gov for glaucoma indications. Many of the emerging treatment modalities are focused on new mechanisms for drug delivery, including sustained-released formulations, surgical implanted drug-eluting devices, and microdosing.[32]

Durysta (Allergan) is Bimatoprost SR (Sustained-Release) implant for treatment of glaucoma and ocular hypertension. This SR delivery system aims to lower IOP for 4 months at a time, is implanted into the anterior chamber, and is biodegradable. This is the first sustained release medication for the treatment of glaucoma.[33]

The Bimatoprost Ring, currently in Phase II and open-label extension, is a silicone and polypropylene ring that is placed in the conjunctival fornix and elutes bimatoprost for up to six months at a time. It can be compared to placement of a contact lens.

iDose (Glaukos) is an innovative hybrid of a MIGS device along with a proprietary formulation of travaprost. It is a less than 2mm titanium implant anchored to Schlemm's canal. Implanting medication in the anterior chamber has the potential to bypass ocular surface side effects of prostaglandin analogues and their preservatives. iDose is currently in Phase III trials.

Piezo-Print Microdose delivery (Eyenovia) is a novel drug delivery system to the ocular surface that disperses medication at the micron level, using electrostatic droplet charging for high-adhesive ocular surface coating. It potentially offers a less toxic and safer way to administer medication, with a 75% reduction in drug dose and preservative delivery to the eye. Phase III trials using latanoprost (MicroProst) are underway.

Also, of note in the Phase III trial is an investigational product combining tafluprost and timolol eye drops (DE-111A, Santen) with planned completion in 2020.[35]

Conclusion

There have been great strides in research and development for the treatment of glaucoma in the last five years, with a focus on decreasing patient morbidity by leveraging the clinical acumen and surgical skill of ophthalmologists. Glaucoma remains a chronic and visually debilitating disease that has vast public health implications, as well as pronounced effects on individual quality of life.

Going forward, development of new modalities to treat glaucoma will continue to align with trends of other ophthalmic indications—novel drug delivery mechanisms and long-acting medications, less invasive surgical procedures, and even gene-based therapy. Thoughtful planning and execution of meaningful and efficient clinical trials are critical to making high-value therapeutics for glaucoma available for patients.

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