Summary of Educational Need & Gap Analysis

Executive Summary

Glaucoma is a leading cause of blindness globally.[1] It affects roughly 64.3 million people, 40 to 80 years of age, worldwide as of 2013, with an expected rise in number to 76 million people by 2020.[2] In the United States, more than 2.5 million people aged 40 years and older currently have primary open-angle glaucoma (OAG).[3] This translates to roughly 2% of the U.S. population with OAG. By 2050, 6.3 million people in the U.S. are predicted to have glaucoma.[4]

Even today, the pathological development of glaucoma is still under investigation.[5] Degeneration of the optic nerve primarily causes the progressive loss of vision in glaucoma.[6] Increased intraocular pressure (IOP) is a major risk factor for the disease and is the only clinically treatable factor that decreases progression of vision loss. Prior clinical trials have shown that, by lowering and tightly controlling the IOP of patients with treatment, vision loss in OAG can be slowed and even prevented.[1] Furthermore, in patients who have a higher than normal IOP (>21 mmHg) with no optic nerve damage, or ocular hypertension (OHT), lowering IOP can reduce the likelihood of future glaucomatous disease.

Due to good patient tolerability and minimal adverse events, topical medications are usually the first step in treatment.[7] The main function of these topical pharmacological agents is to lower the IOP in a patient. When the IOP is insufficiently controlled by medications alone, the doctor then recommends laser or surgical methods to lower the IOP.[3]

Until recently, topical medications for OAG have consisted of the following 5 classes of drugs: prostaglandin analogs, beta-adrenergic receptor antagonists, alpha-2-adrenergic receptor agonists, carbonic anhydrase inhibitors, and cholinergic agonists.[6] Most of these traditional drug classes decrease IOP either by increasing aqueous humor outflow through the uveoscleral pathway or by decreasing aqueous humor production.[1] In a systematic review, prostaglandins were found to be most efficacious at lowering IOP at 3 months compared with the other traditional classes of drugs. However, the adverse effects of eyelash lengthening and iris color change can cause patients to seek alternative therapy.[8] Also, the cholinergic class of drugs increases outflow through the trabecular pathway by way of the ciliary muscle, but the adverse events are intolerable to many patients.[9] Therefore, a subgroup of patients experiences poor IOP control, continual progression of visual field loss events, adverse events, and compliance issues with the traditional glaucoma drugs.[3]

For the first time in 2 decades, new topical drug classes to lower IOP have been developed. The new classes consist of rho-associated kinase (ROCK) inhibitors and modified prostaglandin agents with a nitric oxide-donating moiety.[1] These drugs increase outflow through the trabecular pathway to additively increase IOP lowering and lessen diurnal IOP fluctuations.[9] Of the ROCK inhibitor class, netarsudil 0.02% has become available as of spring 2018, and netarsudil 0.02%/latanoprost 0.005% was approved by the FDA in March 2019.[10] AMA0076 has completed phase 2 clinical trials (NCT02136940, NCT01693315, clinicaltrials.gov). In the modified prostaglandin analog class, latanoprostene bunod 0.024% has been available since late 2017.[11] ONO-9054 has completed a phase 2 trial,[12] and NCX 470 is currently recruiting patients in a phase 2 clinical trial (NCT03657797, clinicaltrials.gov).[13] In a third new class of glaucoma drugs, adenosine agonists, trabodenoson failed a phase 3 trial by not reaching the primary endpoint of superiority in IOP compared with placebo.[14] Based on the recent approval of new therapies and therapies that are in clinical development, optometrists and ophthalmologists need additional

education to be aware of the latest advancements in OAG management. This proposal will address the following gaps in clinician knowledge, namely a lack of familiarity with the new classes of glaucoma drugs.

Title of Initiative	Novel Glaucoma Drugs
Target Audience	Optometrists and Ophthalmologists

Identified Gaps in Practice

Gap 1: Clinicians may not be familiar with the new classes of ROCK inhibitor and modified prostaglandin drugs that have been recently approved or are emerging for the treatment of OAG and OHT.	
Current Practice	First-line treatment of glaucoma consists of hypotensive agents.[5] Since 1996 with the advent of prostaglandin analogs, no new class of glaucoma drugs has made it to phase 3 clinical trials until recently.[1] Even though the prostaglandin analogs are very efficacious and well-tolerated, some patients still experience vision loss and intolerable adverse events.[15,16] None of the 5 traditional classes of glaucoma drugs target the diseased trabecular meshwork (TM), but lower IOP by increasing uveoscleral outflow or decreasing aqueous humor production. Both the new classes of glaucoma drugs, the ROCK inhibitors and modified prostaglandin analogs, target the TM.[1, 15] Clinicians may lack knowledge of the mechanism of action of the new classes of topical glaucoma drugs, ROCK inhibitors and modified prostaglandin analogs, and require additional education on the recent drug approvals and those drugs in late stage trials.
Best Practice	Clinicians will be able to confidently select the appropriate topical therapy for patients with OAG or OHT from all currently available topical glaucoma drugs. They will be able to define the MOA of the new classes of glaucoma drugs, ROCK inhibitors and modified prostaglandin analogs, which have unique properties compared with historical glaucoma drugs.[1,15] Using a drug with a novel MOA may aid in enhancing the mechanical outflow pathway and lowering the IOP further.[9] Careful consideration in selecting a glaucoma drug, weighing their potential advantages and limitations, will aid in better care for the patient.[8]
Learning Objective	Select the most appropriate topical glaucoma drug for patients diagnosed with OAG or OHT.

Appendix: Literature Review Supporting the Educational Need

Glaucoma affects over 64 million people worldwide and causes devastating blindness in many individuals.[2] Since 1996, five classes of hypotensive drugs have been available, all of which display adverse events and limitations. As of today, lowering IOP is the only modifiable risk factor for glaucoma.[15] Fixed-combination or multiple glaucoma medications have been shown to reduce IOP better than monotherapy alone; however, adverse events are still an issue for many patients.[3] Also,

some glaucomatous patients still experience progressive vision loss with traditional glaucoma therapy. Therefore, new and emerging medications for glaucoma patients are warranted.[15]

Gap 1: Clinicians may not be familiar with the new classes of ROCK inhibitor and modified prostaglandin drugs that have been recently approved or are emerging for the treatment of OAG and OHT.

The first line of pharmacological therapy for OAG is usually topical monotherapy with a hypotensive agent.[5] Almost all traditional classes of glaucoma drugs lower IOP by increasing outflow through the uveoscleral pathway or by decreasing production of aqueous humor. However, a main source of untreated pathology in glaucoma has been the trabecular meshwork (TM) and, until recently, this pathology had not been a target of pharmacologic therapy.[18] By not treating the diseased TM through traditional therapies, IOP often increases in patients over time due to further degradation of the TM.[1] With the recent approval of ROCK inhibitors and modified prostaglandin analogs, the TM structure of patients can now be altered, offering an additional pathway to lowering IOP. Clinicians need to be aware of such novel treatments so that they can appropriately select therapies based on their advantages and limitations.

Rho-kinase Inhibitors: Mechanism of Action

The cytoskeleton of the TM and Schlemm's canal cells is a main component in the regulation of aqueous humor drainage. ROCK inhibitors affect the cytoskeleton by rearranging the TM and Schlemm's canal cells' fibers and focal adhesions. This reconfiguring lessens the opposition to TM outflow, thereby lowering IOP.[3]

A potential mechanism of action for ROCK inhibitors is neuroprotection of the retinal ganglion cells (RGCs), which undergo apoptosis extensively in glaucoma patients. In some patients, particularly those with normal tension glaucoma, reduction of IOP alone does not appear to slow progressive visual field loss. By reducing damage to the RGCs, independent of a lowered IOP, the loss of vision may be halted.[5]

In an earlier study, researchers found that oral K-115, a ROCK inhibitor, slowed the death of RGCs in mice and increased the survival of RGC by 34%. Therefore, the findings reveal the potential for ROCK inhibitors to have neuroprotective mechanisms in glaucoma.[5] Researchers also found that ROCK inhibitors improve retinal blood flow by relaxing vascular smooth muscle cells, which then protects neurons. This possible effect on the optic disc blood vessels may also slow progressive visual field loss in glaucoma patients.[19]

Rho-kinase Inhibitors: Clinical Development

Netarsudil

Netarsudil ophthalmic solution 0.02% (netarsudil) is available as of December 2017 for the treatment of OAG and other ocular diseases.[10] Netarsudil is a ROCK inhibitor and a norepinephrine transport inhibitor, which also decreases IOP production.[3] Netarsudil was studied in large, double-blind, noninferiority trials, named Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). In ROCKET-1 and ROCKET-2, netarsudil was found to be clinically and statistically significant in lowering IOP from baseline in patients with a maximum IOP of less than 25 mmHg ($P < .001$).[20]

ROCKET-2 studied 756 patients, with either OAG or OHT, in 3 treatment groups, including netarsudil qd, netarsudil bid and timolol maleate ophthalmic solution 0.5% (timolol) bid. All 3 treatment groups were found to be statistically significant in the mean reduction from baseline IOP of less than 25 mmHg ($P < .0001$, paired *t* test) at all 9 treatment time points. The difference in mean reduction of IOP was 16% to 21%, 22% to 24%, and 18% to 23%, for the group of netarsudil qd, netarsudil bid, and timolol, respectively. Netarsudil qd and netarsudil bid were noninferior to timolol at all 9 time points.[20]

The post hoc endpoint for ROCKET-1 was a baseline IOP of less than 25 mmHg. Netarsudil qd and timolol were found to be clinically and statistically significant in lowering IOP from baseline ($P < .0001$, paired *t* test). Also, netarsudil reached noninferiority to timolol at all 9 time points. The primary efficacy analysis evaluated patients with a baseline of less than 27 mmHg, but netarsudil qd failed to reach the criteria for noninferiority to timolol.[20]

ROCKET-4, also a phase 3 trial, enrolled 608 patients and compared 3-month efficacy and 6-month safety of netarsudil. At 90 days, netarsudil qhs was shown to have a similar reduction of IOP from baseline of less than 25 mmHg and less than 30 mmHg as timolol bid.[15]

A separate study, involving volunteers, analyzed the effects of netarsudil on 24-hour IOP readings, which showed that the reduction in IOP of both the diurnal and nocturnal periods were statistically similar. Nocturnal IOP elevations may cause progression of glaucoma in patients; therefore, this positive finding of netarsudil could be advantageous.[15]

Netarsudil/latanoprost

Netarsudil 0.02%/latanoprost 0.005% (netarsudil/latanoprost), FDA approved in March 2019, is a fixed-dose combination drug that completed phase 3 clinical trials, named MERCURY 1 and MERCURY 2, where it reached primary efficacy endpoint. MERCURY 1 had successful 12-month safety and efficacy results for the fixed-dose combination drug.[21] In MERCURY-1, netarsudil/latanoprost qhs was statistically superior for all 9 time points compared with netarsudil qhs alone and latanoprost qhs alone ($P < .0001$). During the study, the reduction in IOP for the fixed-dose combination was greater by 1–3 mmHg compared with either netarsudil alone or latanoprost alone. At month 3, a greater than or equal to 30% reduction in IOP was 65% in the netarsudil/latanoprost group compared with 29% and 37% in the groups of netarsudil alone and latanoprost alone, respectively ($P < .0001$). Also at month 3, the percentage of patients who reached mean diurnal IOPs of less than or equal to 16 mmHg was 61% in the netarsudil/latanoprost group, compared with 32% and 39% in the groups of netarsudil alone and latanoprost alone, respectively ($P < .0001$).[22]

AMA0076

AMA0076 has completed phase 2 clinical trials. Its unique property is its ability to quickly convert to an inactive form for elimination. This limits the time for adverse events to occur, which may improve patient tolerability.[3] The phase 2 clinical trials were completed to study the safety, tolerability, and efficacy of AMA0076 (NCT02136940, NCT01693315, clinicaltrials.gov); however, the results have not yet been published in the literature. A phase 1 clinical trial for AMA0076 was completed with a total of 82 patients with OAG and OHT. Results from the trial found the mean diurnal IOP for AMA0076 was decreased compared with placebo ($P = .020$ and $P < .005$, respectively).[23] More clinical trials are needed to determine whether AMA0076 can potentially be a new drug medication for the treatment of OAG.[3]

Modified Prostaglandin Analogs: Mechanism of Action

The first choice of treatment for OAG is usually topical prostaglandin analogs due to good efficacy and fewer adverse events compared with other traditional glaucoma drugs.[17] Traditionally, clinicians begin treatment for patients with OAG or OHT with a prostaglandin analog and, if IOP is poorly controlled, then choose an additional drug from the remaining 4 classes of glaucoma drugs.[16] Prostaglandin analogs have an average IOP reduction of 18% to 31% during the day hours and about 8.5% to 17% during the night hours. However, limited efficacy and compliance issues with medications still remain for some patients.[6]

Modified prostaglandin analogs are a new class of drugs that combine the main mechanism of action of prostaglandin analogs, i.e., increasing uveoscleral outflow,[18] with a new mechanism of relaxing the TM through a nitric oxide donation.[3] Therefore, aqueous humor also flows out through the trabecular meshwork which lowers IOP to a greater extent.[3]

Latanoprostene bunod

Latanoprostene bunod 0.024% (LBN), a prostanoid F2-alpha analog, became available in late 2017. When exposed to widespread esterases in the eye, LBN splits into latanoprost acid and butanediol mononitrate, a nitric oxide-donating moeity. The nitric oxide donation is believed to lower IOP by increasing aqueous outflow through the TM and Schlemm's canal; however, further research on butanediol mononitrate could help to determine its specific role in lowering of IOP.[17]

The VOYAGER study, completed in 2012, included 413 patients and revealed that LBN was statistically significant in reduction of the mean diurnal IOP ($P = .005$) and had similar side effects compared with latanoprost 0.005%.[17] In a pooled analysis of 2 phase 3 noninferiority trials (specifically APOLLO and LUNAR), subjects with OAG and OHT had greater reduction in IOP with LBN qd compared with timolol 0.5% bid. Also, subjects treated with LBN sustained a lower IOP through 12 months compared with timolol 0.5% bid. LBN had a mean IOP that was significantly lower at all 9 timepoints during the efficacy phase compared with timolol ($P < .001$). Subjects treated with LBN significantly reached a mean IOP of less than or equal to 18 mmHg and IOP reduction of greater than or equal to 25% from baseline compared with subjects treated with timolol ($P < .001$).[24]

The JUPITER study evaluated 121 Japanese subjects with OAG or OHT given LBN qhs over a 52-week period. LBN caused a 26% reduction in IOP from baseline at 52 weeks with a mean of 14.4 mmHg. This indicates that continued treatment with LBN could reduce IOP long-term.[9]

ONO-9054

ONO-9054 has completed a phase 2 trial. It is a new compound that targets both the prostanoid F receptor and the prostanoid EP3 receptors, which are found in the TM and ciliary muscle. This targeting action of the EP3 receptors increases the outflow of aqueous humor through the TM pathway, which adds to the outflow of the uveoscleral pathway through the mechanism of the prostaglandin analog for a more effective lowering of IOP.[3] The results of the phase 2 clinical trial, which included 62 subjects, revealed that ONO-9054 had a better reduction in mean diurnal IOP compared with latanoprost (-7.2 mmHg versus -6.6 mmHg). Also, the percentage of subjects who reached target IOPs on day 29 was greater with ONO-9054 treatment compared with latanoprost treatment. In obtaining an IOP less than or equal to 15 mm Hg, the odds for ONO-9054 were 2.4 times greater than the odds for latanaprost (*P*

< .01, post hoc analysis).[12] Larger clinical trials that study the efficacy of ONO-9054 for the treatment of OAG and OHT is warranted by the positive results from the phase 2 trial.

NCX 470

NCX 470 is a nitric-oxide donating bimatoprost analog that will begin a phase 2 trial in 2018.[13]

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