Off Label Innovation: Discovering New Uses for Glaucoma Drops

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Neovascular age-related macular degeneration (nAMD) is a common retinal disease that is the leading cause of blindness in the United States.[1] Neovascularization is the process of uncontrolled, progressive growth of aberrant blood vessels in the back of the eye. These weak vessels can leak intravascular fluid that may ultimately damage the macula, the central area of the retina that is responsible for sharp, central, color vision. Intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) agents is currently the gold standard treatment to reduce the growth of and leakage from new blood vessels, thereby slowing nAMD progression.[1]

Most clinicians follow a treat and extend protocol when injecting anti-VEGF drugs.[2] Patients are typically initiated on injections at monthly intervals. Once the edema is under control, the injection intervals are gradually increased until signs of exudation recur, at which point the next interval is decreased to the prior interval without exudation. This protocol generally helps to minimize the number of injections for patients while maximizing visual outcomes, and the average patient typically ends up requiring injections approximately every 2 - 3 months for maintenance once stabilized.[3,4] However, some patients have a suboptimal response to the currently available anti-VEGF drugs and demonstrate persistent exudation despite frequent injections at 4 - 6 week intervals.

A few studies suggest that anti-VEGF injections are cleared through aqueous humor outflow in the anterior chamber of the eye.[6-8] As a result, it has been hypothesized that reducing aqueous humor production may reduce fluid and drug turnover inside the eye, allowing anti-VEGF agents to have a longer duration of effect.[6-8] Dr. Jason Hsu worked on a case series in which patients with nAMD who were suboptimal responders to anti-VEGF had less signs of exudation after being started on topical dorzolamide-timolol, a carbonic-anhydrase inhibitor and beta-blocker combination used to treat glaucoma.[9] Dorzolamide-timolol has a potent effect on reducing aqueous humor production by 50%, and its components may also downregulate VEGF production. In addition, some studies have shown that its components may help reduce cystoid macular edema and increase retinal perfusion and oxygenation that could further benefit patients with nAMD.[10-15]

Dr. Jason Hsu and his team (Ophthalmic Consultants of Boston, Boston, Massachusetts; Retinal Consultants of Houston, Houston, Texas; Retina Service of Wills Eye Hospital and Mid Atlantic Retina, Philadelphia, Pennsylvania; Associated Retinal Consultants, Royal Oak, Michigan) performed a multicenter

randomized placebo-controlled clinical trial in which patients with nAMD who were suboptimal responders despite frequent anti-VEGF injections were randomized to use either dorzolamide-timolol drops or artificial tears.[16] Eligible patients were 45 years or older with nAMD who were receiving ranibizumab or aflibercept injections at 4 - 6 week intervals (i.e., at least four injections within six months prior to enrollment) and had evidence of persistent exudation, which was defined as intraretinal or subretinal fluid on optical coherence tomography (OCT). They must have received the same anti-VEGF agent for two consecutive visits with an injection interval of 4 - 6 weeks. Finally, the patients needed a baseline central subfield thickness (CST) of at least 270 µm on OCT.

Sixty-three eligible patients were subsequently randomized to the twice-daily treatment of dorzolamide-timolol or to the placebo of artificial tears. The physicians and study coordinators were blinded. OCT, visual acuity, and intraocular pressure (IOP) measurements were taken at each of the three visits. The primary outcome was change in CST, an automated measurement that represents the average macular thickness within a 1 mm circle centered on the fovea. Secondary outcomes included changes in maximum subretinal fluid height (SRF), maximum pigment epithelial detachment (PED), central foveal thickness (CFT), central subfoveal fluid height (CFF), mean visual acuity, and IOP. There were 27 patients in the experimental group and 23 in the placebo group that completed the third visit after three months in the study.

Regarding anatomical outcomes, the study showed significant improvements in mean CST and maximum PED height. Changes in maximum SRF height, CFT, and central SFF height were not significant. Changes in logMAR visual acuity and IOP were also not significant. The study concluded that topical dorzolamide-timolol treatment in nAMD patients with persistent exudation reduced macular edema but did not significantly change visual acuity. Perhaps more research on the clinical relevance of these anatomical changes or a longer study duration may better illustrate the effects of dorzolamide-timolol on nAMD. Through this study's use of randomization, a control group, and blinding, it effectively builds on the growing literature of case reports and non-randomized trials using dorzolamide-timolol drops as an adjunct to anti-VEGF therapy for patients with nAMD. Thus, it can be concluded that dorzolamide-timolol's use as an adjunctive therapy is effective for reducing macular edema in the treatment of nAMD.

When we interviewed Dr. Hsu on the

Dr. Jason Hsu
Credit: Wills Eye Hospital

development of this study, he explained that the first patient who benefited from the use of glaucoma drops was a colleague with a history of anti-VEGF injections. Almost immediately after initiation of the adjuvant therapy, Dr. Hsu observed a significant amount of fluid reduction. As a result, a pilot study was initiated and, based on the promising results, led to the multicenter randomized clinical trial. I found this clinical trial especially interesting because it highlighted a medical innovation in an unexpected way. Discovering new techniques or pharmacologic therapies is clearly important for medical progress, but finding alternative uses and maximizing the potential of existing therapies is equally innovative. Retinal diseases, including nAMD, often do not consider topical therapy. Dr. Hsu and his team's use of topical dorzolamide-timolol is a noteworthy innovation that will make an impact on many patients suffering with nAMD.

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