Original Investigation

Topical Dorzolamide-Timolol With Intravitreous Anti–Vascular Endothelial Growth Factor for Neovascular Age-Related Macular Degeneration

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IMPORTANCE There is a subset of eyes with neovascular age-related macular degeneration (AMD) that have persistent exudation despite fixed-interval intravitreous anti–vascular endothelial growth factor (VEGF) injections.

OBJECTIVE To evaluate the effect of topical dorzolamide hydrochloride–timolol maleate on anatomic and functional outcomes in eyes with neovascular AMD and incomplete response to anti-VEGF therapy.

DESIGN, SETTING, AND PARTICIPANTS An exploratory, prospective single-arm interventional study at a tertiary referral academic private practice. Patients with neovascular AMD and persistent macular edema despite fixed-interval intravitreous anti-VEGF therapy were enrolled. Baseline spectral-domain optical coherence tomography and clinical data, including visual acuity and intraocular pressure, were obtained at enrollment and from one visit before enrollment. The study was performed at the Retina Service of Wills Eye Hospital and the offices of Mid Atlantic Retina from February 1, 2015, through September 30, 2015. Patients were followed up for at least 2 visits after enrollment. Central subfield thickness, maximum subretinal fluid height, and maximum pigment epithelial detachment height from spectral-domain optical coherence tomography were recorded at each visit.

INTERVENTIONS Enrolled eyes received a regimen of topical dorzolamide-timolol twice daily and continued to receive the same intravitreous anti-VEGF therapy at the same interval as received before enrollment for the duration of the study.

MAIN OUTCOMES AND MEASURES Change in central subfield thickness was the primary outcome measure. Changes in maximum subretinal fluid height, maximum pigment epithelial detachment height, and visual acuity were the secondary outcome measures.

RESULTS Ten patients (10 eyes) completed the study. The mean age of the patients was 78.2 years (age range, 65-91 years), and 6 were male. Eight eyes received intravitreous aflibercept, and 2 eyes received intravitreous ranibizumab. All study eyes had been receiving long-term anti-VEGF therapy with the same medication before study enrollment for a mean of 21.9 injections. The mean central subfield thickness decreased from 419.7 μm at enrollment to 334.1 μm at the final visit (P = .01). The mean maximum subretinal fluid height decreased from 126.6 μm at enrollment to 49.5 μm at the final visit (P = .02). The mean maximum pigment epithelial detachment height decreased from 277.4 μm at enrollment to 239.9 μm at the final visit (P = .12). The mean logMAR visual acuity were 0.54 at enrollment and 0.48 at the final visit (P = .60).

CONCLUSIONS AND RELEVANCE These data suggest that topical dorzolamide-timolol may reduce central subfield thickness and subretinal fluid in eyes with persistent exudation despite consistent, fixed-interval intravitreous anti-VEGF treatment for neovascular AMD.

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Intravitreous anti–vascular endothelial growth factor (VEGF) agents, including bevacizumab, ranibizumab, and aflibercept, remain the standard-of-care treatment for neovascular age-related macular degeneration (AMD).[1-4] Various treatment modalities using these agents have been proposed, including monthly, pro re nata, and treat-and-extend regimens.[5,6] Despite frequent and consistent treatment with anti-VEGF therapy, there is a subset of patients who are incomplete responders and have persistent exudation, including intraretinal edema, subretinal fluid (SRF), or retinal pigment epithelial detachment (PED) on spectral-domain optical coherence tomography (SD-OCT).[7,8]

While the clearance of intravitreous anti-VEGF drugs is not completely understood, the results of some studies[9-12] have suggested that outflow through the anterior chamber may have a role. We hypothesized that, by decreasing aqueous production, the outflow may also be reduced, which could subsequently slow the clearance of intravitreous drugs. This study aimed to evaluate the effect of topical dorzolamide hydrochloride-timolol maleate, a potent and readily available aqueous suppressant,[13] on anatomic and functional outcomes in incomplete anti-VEGF responders with neovascular AMD.

Key Points

Question: Could topical dorzolamide hydrochloride–timolol maleate reduce central subfield thickness (CST) in patients with neovascular age-related macular degeneration (AMD) and persistent exudation despite anti–vascular endothelial growth factor (VEGF) therapy?

Findings: This exploratory study that included 10 eyes showed that the addition of topical dorzolamide-timolol to fixed-interval anti-VEGF therapy for neovascular AMD with persistent exudation resulted in a significant decrease in CST and subretinal fluid (SRF) as measured on spectral-domain optical coherence tomography.

Meaning: The results suggest that topical dorzolamide-timolol in combination with anti-VEGF injections may further reduce CST and SRF in eyes with persistent exudation from neovascular AMD.

Methods

Wills Eye Hospital Institutional Review Board approval was obtained for this prospective single-arm interventional study evaluating the effect of topical dorzolamide-timolol on eyes with neovascular AMD with persistent exudation seen on SD-OCT despite fixed-interval intravitreous anti-VEGF injections. The study was performed at the Retina Service of Wills Eye Hospital and the offices of Mid Atlantic Retina from February 1, 2015, through September 30, 2015. All participants gave written informed consent for completion of the study protocol as detailed below and collection of demographic and historical data before enrollment. The study was conducted in accord with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki.[14] The study was registered at clinicaltrials.gov under the identifier NCT02571972.

Patients with neovascular AMD who were incomplete responders to intravitreous anti-VEGF therapy were eligible for enrollment. We defined incomplete responders as eyes having evidence of intraretinal edema or SRF on SD-OCT (Spectralis HRA + OCT; Heidelberg Engineering, Inc) at each of at least 4 prior visits within a 6-month period despite intravitreous anti-VEGF injections at each visit. Study eyes were also required to have been receiving the same anti-VEGF drug (bevacizumab, ranibizumab, or aflibercept) and to have been on an identical fixed treatment interval of 4, 5, or 6 weeks for at least 2 visits before study enrollment. Exclusion criteria for study eyes included history of uveitis, pars plana vitrectomy, glaucoma surgery, any other eye surgery (including cataract extraction) in the 6 months before enrollment, as well as history of topical antiglaucoma therapy, history of sulfonamide allergy, concomitant systemic diuretic or corticosteroid use, and any systemic contraindications to topical β-blocker therapy (including history of reactive airway disease, bradycardia, or decompensated heart failure).

Baseline data were recorded, including age, sex, study eye, medical and ocular history, visual acuity (VA), intraocular pressure (IOP) measurement using a tonometer (Tono-Pen XL; Reichert Inc), dilated fundus examination findings, and SD-OCT results. On the day of enrollment, study eyes received an injection of the same intravitreous anti-VEGF drug that had been given at the prior 2 or more office visits. Patients were then provided topical dorzolamide-timolol and instructed to instill the eyedrops twice daily in the study eye for the duration of the study period. The patients then returned at the same interval as before study enrollment for 2 subsequent office visits. At each of these visits, VA testing, IOP measurement, SD-OCT imaging, and intravitreous anti-VEGF injection with the same drug used at the prior visit were performed. Compliance with topical therapy was verified at each visit by patient reporting.

The SD-OCT images from the visit before enrollment, the study enrollment visit, and each subsequent study visit were analyzed. Automated central subfield thickness (CST) measurements were generated from the 25-line raster scan pattern protocol using a software package (Heidelberg Eye Explorer; Heidelberg Engineering, Inc). The line raster scans from the enrollment visit were examined, and the maximum SRF height was manually measured using the caliper tool in the software package from the outer retina to the hyperreflective line of the retinal pigment epithelium. A similar process was repeated to identify and measure the maximum retinal PED height from the peak of the hyperreflective line of the retinal pigment epithelium to the hyperreflective line of Bruch membrane. The software package's SD-OCT tracking feature enabled sequential scans to be captured in identical locations, providing accurate assessment of CST, SRF height, and PED height on follow-up visits. A single examiner (J.S.) who is experienced at analyzing SD-OCT scans performed the manual measurements.

The primary outcome measure was change in CST. The secondary outcome measures included change in VA, maximum SRF height, and maximum PED height. Best-available Snellen VAs (present correction with pinhole) were converted to logMAR equivalents for statistical analyses. Statis-

tical analysis with paired *t* test (GraphPad; GraphPad Software Inc) was used to analyze for change in VA, IOP, CST, maximum SRF height, and maximum PED height between visits. Statistical significance was set at $P < .05$.

Results

Fourteen patients (15 eyes) were enrolled. Two patients (2 eyes) chose never to start topical dorzolamide-timolol therapy. Two other patients (3 eyes) received dorzolamide-timolol for the duration of the study period, but each patient had one study visit with a variable follow-up interval due to patient rescheduling, which could have biased the results. As a result, these eyes were excluded from the final data analysis.

Ten patients (10 eyes) completed the study per protocol. Baseline demographic characteristics are listed in **Table 1.** All study eyes had been receiving long-term anti-VEGF therapy with the same medication before study enrollment for a mean of 21.9 injections (range, 7-32 injections). There were no differences in CST, maximum SRF height, or maximum PED height from the visit immediately before enrollment compared with the study enrollment visit (**Table 2**).

Table 1. Baseline Demographic Characteristics

Variable	Value (N = 10)
Age, mean (range), y	78.2 (65-91)
Male sex, No.	6
Eyes, No.	10
Right eyes, No.	5
Intravitreous anti-VEGF agent, No.	
Aflibercept	8
Ranibizumab	2
Prior injections with the same anti-VEGF, mean (range), No.	21.9 (7-32)
Pseudophakic, No.	8
Current treatment interval, No.	
Every 4 wk	8
Every 5 wk	1
Every 6 wk	1

Abbreviation: VEGF, vascular endothelial growth factor.

The CST, maximum SRF height, and maximum PED height results for each study visit are also listed in Table 2. All patients completed at least 2 study visits, and 8 patients completed a third study visit. Of the 2 eyes of 2 patients who did not have a standardized additional third visit, one patient chose to stop the eyedrops, and one patient had not returned for the third visit. The mean CST decreased from 419.7 µm at enrollment to 334.1 µm at the final visit ($P = .01$), with the decrease noted at the first visit after enrollment. All 10 eyes had a decrease in CST at the final visit compared with enrollment. The mean maximum SRF height decreased from 126.6 µm at enrollment to 49.5 µm at the final visit ($P = .02$), with the decrease noted at the first visit after enrollment. All 10 eyes had a decrease in maximum SRF height at the final visit compared with enrollment, with complete resolution of SRF in 4 of 10 eyes. The mean maximum PED height decreased from 277.4 µm at enrollment to 239.9 µm at the final visit ($P = .12$). Five of the 10 eyes had a decrease in maximum PED height at the final visit compared with enrollment. A similar analysis of the full cohort of 13 eyes who used dorzolamide-timolol showed similar findings (eTable in the Supplement). **Figure 1** and **Figure 2** show the SD-OCT changes during the course of the study in 2 of these patients.

There was no change in the mean logMAR VA from the enrollment visit (mean [SD], 0.54 [0.53]) to the final visit (mean [SD], 0.48 [0.29]) ($P = .60$). The mean IOP decreased from the enrollment visit to the final visit (from 14.5 to 11.9 mm Hg, $P = .08$).

Discussion

The results of prior studies[7,15] have suggested that up to 15% of patients with neovascular AMD may be incomplete responders to intravitreous anti-VEGF therapy. A variety of strategies have been proposed to help these patients, including combination treatment with photodynamic therapy, combination

Table 2. Anatomic Outcomes[a]

	Mean (SD), µm					
Variable	CST	*P* Value	Maximum SRF Height	*P* Value	Maximum PED Height	*P* Value
Preenrollment visit (N = 10)	422.9 (100.9)	NA	111.5 (101.3)	NA	275.4 (170.7)	NA
Enrollment visit (N = 10)[b]	419.7 (95.9)	.81	126.6 (78.2)	.37	277.4 (174.9)	.80
Study visit 1 (N = 10)[c]	364.5 (76.3)	.007	77.9 (70.7)	.04	258.9 (173.7)	.20
Study visit 2 (N = 10)[d]	346.7 (99.9)	.03	62.0 (59.7)	.03	227.8 (163.0)	.13
Study visit 3 (n = 8)[e]	326.9 (115.5)	.03	56.5 (58.0)	.05	275.4 (160.8)	.18
Final visit (N = 10)[f]	334.1 (103.0)	.01	49.5 (54.2)	.02	239.9 (163.0)	.12

Abbreviations: CST, central subfield thickness; NA, not applicable; PED, pigment epithelial detachment; SRF, subretinal fluid.

[a] *P* values are by paired *t* test. Eight of 10 eyes completed a third study visit. Final visit data include data from study visit 3 for 8 eyes and data from study visit 2 for the 2 eyes that did not complete a third study visit.

[b] *P* values are based on comparison of the enrollment visit with the preenrollment visit.

[c] *P* values are based on comparison of study visit 1 with the enrollment visit.

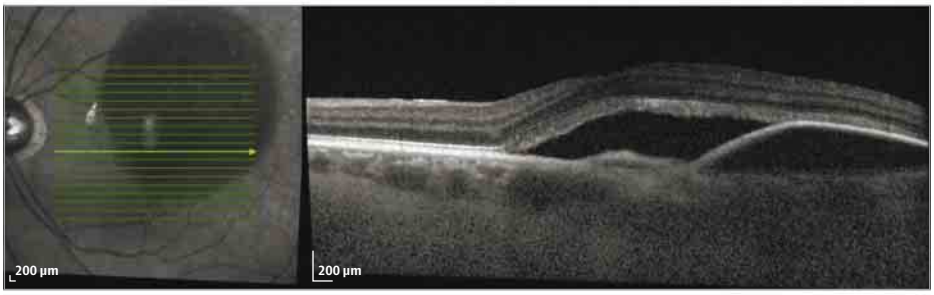
[d] *P* values are based on comparison of study visit 2 with the enrollment visit.

[e] *P* values are based on comparison of study visit 3 with the enrollment visit.

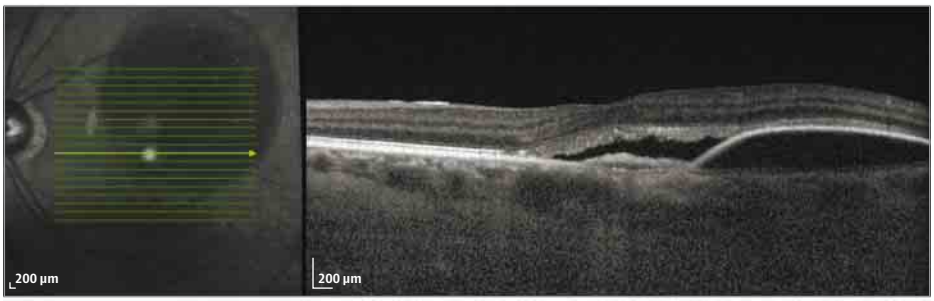
[f] *P* values are based on comparison of the final visit with the enrollment visit.

Figure 1. An 81-Year-Old Man With Neovascular Age-Related Macular Degeneration

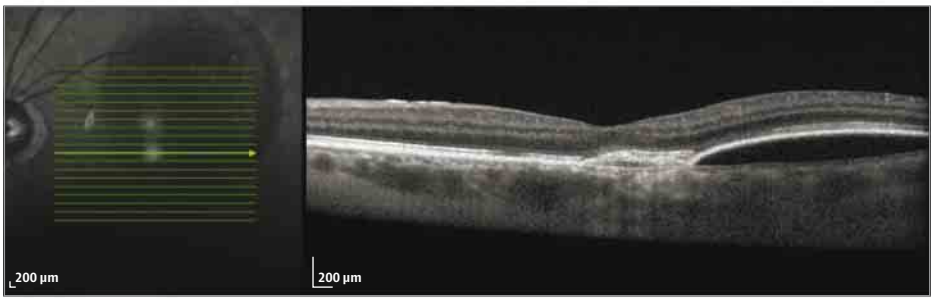
A Topical dorzolamide hydrochloride-timolol maleate commencement at this visit



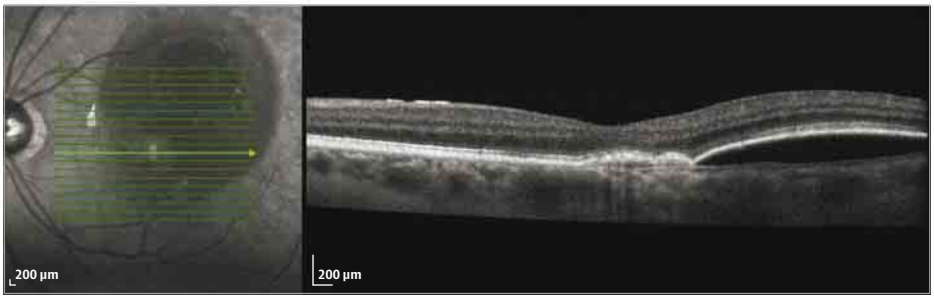
B Month 1 follow-up



C Month 2 follow-up



D Month 3 follow-up

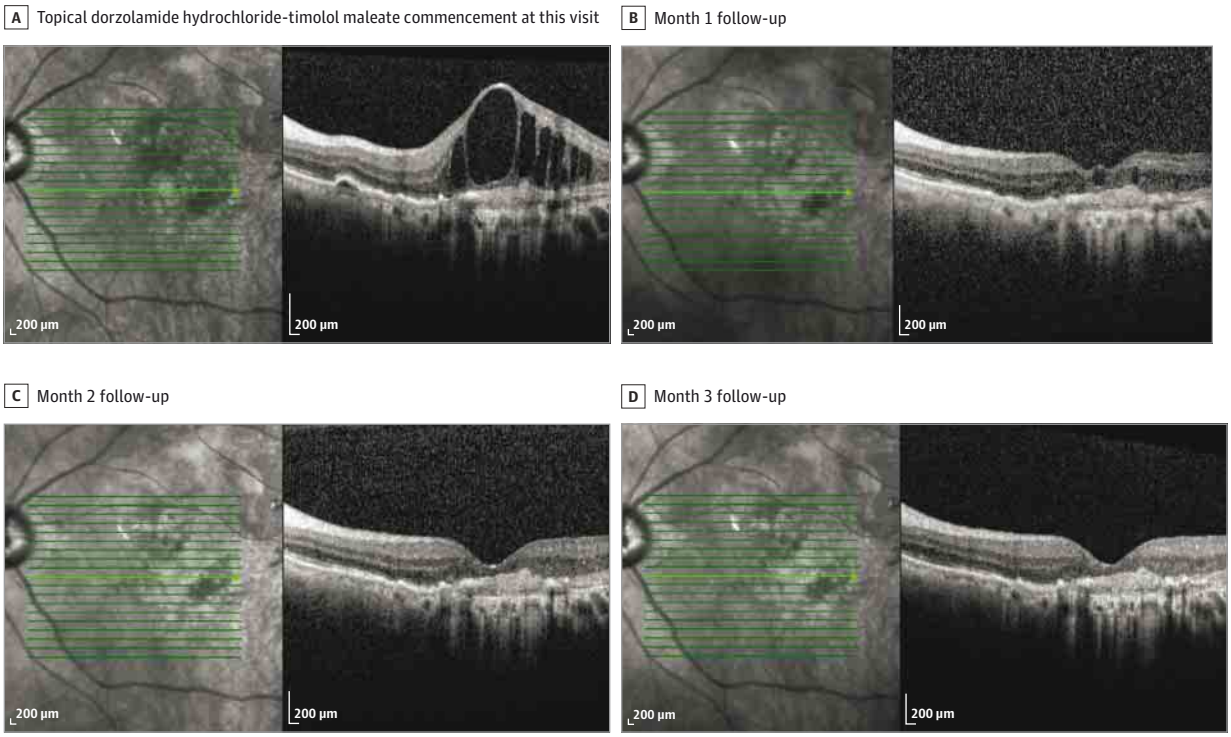


A, The patient had persistent subretinal fluid despite monthly intravitreous aflibercept and started receiving topical dorzolamide hydrochloride–timolol maleate. B-D, On monthly follow-up, subretinal fluid decreased (B and C) until ultimately resolving (D). The spectral-domain optical coherence tomography image through the foveal center is shown in the right panel. The corresponding infrared fundus image is shown in the left panel, with the bold horizontal arrow referencing the area segmented. The same area was segmented for each visit.

therapy with intravitreous corticosteroids, biweekly anti-VEGF dosing algorithms, and combination therapy with topical nonsteroidal anti-inflammatory eyedrops.[16-19] However, topical aqueous suppression with dorzolamide-timolol in combination with anti-VEGF therapy appears to represent a novel strategy for treating incomplete responders or nonresponders with neovascular AMD.

One possible mechanism for the efficacy of topical dorzolamide-timolol as an adjuvant to intravitreous anti-VEGF is its aqueous suppressant properties.[9,13] Dorzolamide-timolol has been shown to reduce aqueous flow by approximately 50%.[13] Although the exact mechanism by which intravitreous anti-VEGF agents are cleared from the eye is not clearly understood, there is evidence that outflow through the ante-

Figure 2. A 70-Year-Old Man With Neovascular Age-Related Macular Degeneration



A, The patient had persistent macular edema despite monthly intravitreous aflibercept and started receiving topical dorzolamide hydrochloride–timolol maleate. B-D, On monthly follow-up, macular edema decreased (B and C) until ultimately resolving (D). The spectral-domain optical coherence tomography image through the foveal center is shown in the right panel. The corresponding infrared fundus image is shown in the left panel, with the bold horizontal arrow referencing the area segmented. The same area was segmented for each visit.

rior chamber may have a role.[10,11] For example, ranibizumab concentrations in the aqueous humor are much lower than in the vitreous but appear to decline in parallel with vitreous levels.[12] This finding suggests that one of the main routes of elimination may be via aqueous outflow. As a result, decreasing aqueous production may reduce the outflow of fluid from the eye, thereby prolonging the half-life of the anti-VEGF drug. One clinical study[9] that supports this hypothesis was performed in patients receiving a single intravitreous bevacizumab injection for the treatment of macular edema due to branch or central retinal vein occlusion. Patients were randomly assigned to receive topical dorzolamide-timolol eyedrops or no eyedrops. The mean central retinal thickness decreased in both groups at 1 week after injection, but by 5 weeks the dorzolamide-timolol group had a lower mean central retinal thickness (P = .03). However, by 9 weeks there was no difference between the 2 groups. The authors concluded that the aqueous suppressant may have delayed the clearance of the bevacizumab.

Although there was no change in VA in our study, it has been argued that VA does not provide the best assessment of visual function in patients with AMD.[20] In addition, the improvement in macular edema on OCT often precedes VA improvement.[21,22] Because the present investigation was a study of short duration, it is possible that longer-duration topical therapy may show VA benefit. The further decline in CST and SRF at the third study visit for the 8 eyes that remained on dorzolamide-timolol therapy suggests that there may be added benefit over time. Given that all patients had chronic persistent exudation, despite regular fixed-interval anti-VEGF injections, it is also possible that permanent microstructural damage may be the limiting factor for VA recovery in spite of the reduction in CST and SRF. It may be that starting topical dorzolamide-timolol earlier in the course of anti-VEGF treatment for these incomplete responders may provide more functional benefit.

Besides decreasing aqueous outflow, it is possible that either the β-blocker (timolol maleate) or carbonic anhydrase inhibitor (dorzolamide hydrochloride) components may have had direct effects via alternative mechanisms. It has been previously demonstrated in a mouse model for retinopathy of prematurity that β-adrenergic blockade reduced upregulation of VEGF and decreased hypoxic retinopathy.[23] Additional studies[24,25] in the mouse model revealed that β_2-adrenergic receptor blockade was primarily responsible for the reduced levels of angiogenic factors and retinal neovascularization. Furthermore, β-adrenergic blockade has been shown to specifically attenuate choroidal neovascularization and reduce VEGF expression.[26] One retrospective case series reported that patients with neovascular AMD taking systemic β-adrenergic blocking agents were statistically more likely to receive fewer intravitreous injections of bevacizumab than their counter-

parts not receiving the systemic therapy.[27] However, the Beaver Dam Eye Study[28] found that oral β-blocker treatment was associated with a 71% increased hazard of incident exudative AMD, arguing against a protective effect. Moreover, a recent retrospective study[29] demonstrated that there was no difference in the rate of β-blocker use between matched patients with exudative and nonexudative AMD. The authors concluded that systemic β-blockers are not protective against choroidal neovascularization, possibly due to the lower administered dosage compared with animal models. It is possible that topical delivery of β-blockers may yield a higher intraocular drug concentration than systemic exposure, supporting the concept that direct β-blockade by timolol could have had a contributing role in our study. However, there is insufficient clinical evidence based on the present study or the current literature to fully support this theory.

Dorzolamide has been used successfully in the treatment of macular edema due to various causes, including retinitis pigmentosa, X-linked retinoschisis, and choroideremia.[30-33] Membrane-bound carbonic anhydrase enzyme has been confirmed in Müller cells and retinal pigment epithelial cells.[34,35] Carbonic anhydrase inhibition may modulate Müller cell activity and retinal pigment epithelial pump function, leading to fluid egress from the retina to the choroid and therefore reduced edema.[34,35] Dorzolamide may also increase retinal and choroidal perfusion.[36,37] Harris et al[37] reported more rapid arteriovenous transit time on fluorescein angiography in patients taking topical dorzolamide-timolol compared with topical timolol alone. In addition, systemic dorzolamide has been demonstrated to increase retinal oxygenation in an animal model for branch retinal vein occlusion.[38] One study[39] described increased short-wavelength automated perimetry sensitivity in patients with nonexudative AMD receiving topical dorzolamide vs placebo, perhaps secondary to improved choroidal or retinal blood flow. Therefore, it is possible that the dorzolamide component alone may have had an independent role in reducing the macular edema.

Our study has several limitations, including the small sample size and short duration of dorzolamide-timolol treatment. In addition, we are not able to distinguish whether the beneficial effect seen in this study was a result of dorzolamide, timolol, or a combination of the two. A future prospective study using each individually compared with the combination would be helpful to further define which drug contributed to the positive effects we observed. Another limitation was the use of different intravitreous anti-VEGF agents, although most patients received aflibercept. Normal fluctuations in disease activity could have also accounted for the changes in CST and SRF height seen during the study period. However, we chose to enroll patients who had been receiving chronic fixed-interval therapy with the same medication. By comparing data from the visit before enrollment with data from the enrollment visit, we demonstrated that the disease activity was fairly stable until dorzolamide-timolol was introduced. Moreover, despite keeping all other variables the same (eg, drug choice and interval between injections), the decrease in CST was noted as early as the first visit after starting the topical eyedrops and was maintained for the duration of the study, with a gradually decreasing mean CST over time. An additional limitation is that patient compliance with dorzolamide-timolol use was dependent on self-reporting, although the decrease in the mean IOP suggests that patients were using the topical therapy. The use of a tonometer may have also affected the accuracy of our IOP measurements. Finally, we relied on the manual measurements of SRF and PED heights rather than automated computer algorithms, which may have introduced bias. However, our CST measurements were automated and showed a clear mean decrease over time after starting the topical eyedrops, arguing against the introduction of bias.

Conclusions

These data suggest that topical dorzolamide-timolol adjuvant treatment may reduce CST and maximum SRF height in eyes with persistent exudation on SD-OCT despite fixed-interval chronic intravitreous anti-VEGF treatment for neovascular AMD. No differences in VA or maximum PED height were identified during this short-term study. A larger study with longer-duration topical therapy would be helpful to confirm the clinical value of this adjuvant therapy. It may be that, with earlier topical eyedrop initiation and longer-duration therapy, additional clinical benefits may be found, such as VA gains or less frequently required anti-VEGF injections.

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Study concept and design: Sridhar, Hsu.
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Drafting of the manuscript: Sridhar.
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