SDC

# EFFECT OF INTRAOCULAR PRESSURE–LOWERING MEDICATIONS ON NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATMENT OUTCOMES IN THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENT TRIALS

EHSAN RAHIMY, MD,*† GUI-SHUANG YING, PHD,‡ WEI PAN, MS,‡ JASON HSU, MD,† ON BEHALF OF THE CATT RESEARCH GROUP

**Purpose:** To evaluate the effect of intraocular pressure-lowering medications on treatment outcomes in the Comparison of AMD Treatments Trials.

**Methods:** Secondary analysis of Comparison of AMD Treatments Trials data. Medication logs were reviewed for continuous 2-year use of agents that increased aqueous outflow (Group A: topical prostaglandins) or suppressed aqueous production (Group B: topical beta blockers and carbonic anhydrase inhibitors). Eyes were excluded if mixed-mechanism intraocular pressure–lowering agents or medications from more than one group were taken. Anatomical and vision responses to treatment at years 1, 2, and over the entire 2-year period in each group were compared with controls (no intraocular pressure–lowering medications).

**Results:** Inclusion criteria were met by 28 Group A patients, 19 Group B patients, and 857 controls. After 2 years, the control group had a mean visual acuity improvement of +6.3 letters from baseline, compared with +3.5 letters in Group A ($P = 0.38$), and +13.8 letters in Group B ($P = 0.052$). Mean retinal thickness change from baseline was $-54.9$ $\mu$m in controls, $-80.6$ $\mu$m in Group A ($P = 0.26$), and $-96.8$ $\mu$m in Group B ($P = 0.13$). Mean total thickness change from baseline was $-163$ $\mu$m in controls, $-180$ $\mu$m in Group A ($P = 0.63$), and $-238$ $\mu$m in Group B ($P = 0.08$). In longitudinal analysis with adjustment by their baseline values, anti–vascular endothelial growth factor treatment drug and regimen, Group B had more visual acuity improvement (difference of 2.6 letters, 95% confidence interval: $-3.4$–8.5 letters), more reduction in the retinal thickness ($-17.9$ $\mu$m, 95% confidence interval: $-36.5$ to 0.7 $\mu$m), and total thickness from baseline (mean difference of $-54.7$ $\mu$m, 95% confidence interval: $-103$ to 6.2 $\mu$m) compared with the control group.

**Conclusion:** Concurrent aqueous suppressant use during anti–vascular endothelial growth factor therapy for neovascular age-related macular degeneration was associated with a trend toward greater reductions in retinal and total thickness as well as improved visual outcomes over 2 years. A similar effect was not observed to the same extent with agents that increase aqueous outflow. Because of the small sample size and secondary analysis, these findings must be cautiously interpreted and perhaps serve as a basis for future prospective studies.

**RETINA** 0:1–12, 2018

The class of vascular endothelial growth factor (VEGF) inhibitors, including bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea; Regeneron, Tarrytown, NY), has revolutionized the treatment of neovascular age-related macular degeneration (AMD) and remains the standard of care in managing this disease.[1–7] Although ongoing therapy over

many years is typically required, the treatment intervals can vary widely from patient to patient, raising interest in understanding this variability, including elucidating the mechanisms underlying the clearance of anti-VEGF agents within the eye.

Several studies have implicated aqueous outflow through the anterior chamber as contributing to the intraocular clearance of VEGF inhibitors.[8–11] Suppressing aqueous humor production could reduce the aqueous outflow, which may in turn decrease drug clearance and thereby prolong the effect of intravitreally administered pharmacotherapies.[12] This was supported by a recent pilot study, which demonstrated that adjuvant treatment with topical dorzolamide–timolol had a synergistic effect on reducing subretinal fluid (SRF) and central subfield thickness measurements in eyes with persistent exudation due to neovascular AMD despite consistent, fixed-interval anti-VEGF injection schedules.[12] These findings have led to increased interest in investigating the potential effects of additional intraocular pressure (IOP)–lowering medications on treatment outcomes in neovascular AMD.

The Comparison of AMD Treatments Trials (CATT) was a 2-year study that evaluated the efficacy of ranibizumab compared with bevacizumab, as well as monthly compared with as needed treatments in 1,185 patients,[5,6] and provides an opportunity to perform an observational analysis comparing functional and anatomical outcomes from a subpopulation of patients simultaneously using IOP-lowering agents during the study period with controls.

## Methods

Details of the CATT study design and methods have been previously published, and are available on ClinicalTrials.gov (identifier, NCT00593450).[5,6] Only the major features related to this secondary data analysis are described here.

From the *Department of Ophthalmology, Palo Alto Medical Foundation, Palo Alto, California; †The Retina Service of Wills Eye Hospital, Mid Atlantic Retina, Philadelphia, Pennsylvania; and ‡Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Supported by NIH U10 EY0\17823, U10 EY017825, U10 EY017826, U10 EY017828 and R21EY023689.

None of the authors has any financial/conflicting interests to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

Reprint requests: Jason Hsu, MD, Mid Atlantic Retina, The Retina Service of Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA 19107; e-mail: jhsu@midatlanticretina.com

### *Study Participants*

The institutional review board associated with each clinical center approved the study protocol, and informed consent was obtained from each participating patient. The inclusion criteria were age ≥50 years, untreated active choroidal neovascularization (CNV) resulting from AMD in the study eye (1 eye per patient), and visual acuity between 20/25 and 20/320 on electronic visual acuity testing.[5,6] Determination of active CNV required both leakage of dye on fluorescein angiography and the presence of fluid (intraretinal fluid, SRF, or sub-retinal pigment epithelium [RPE]) on time-domain optical coherence tomography (OCT).

Patients were enrolled from 43 clinical centers in the United States and randomized to one of 4 treatment groups at baseline: 1) ranibizumab monthly, 2) bevacizumab monthly, 3) ranibizumab as needed (pro re nata [PRN]), or 4) bevacizumab PRN. At the end of Year 1, patients initially assigned to monthly treatment retained their original drug assignment but were reassigned randomly to either monthly or PRN treatment. Patients initially assigned to PRN treatment retained both their same drug and regimen for Year 2.

### *Study Procedures*

During the initial visit, patients provided information regarding demographic characteristics and medical history. Stereoscopic color fundus photography and fluorescein angiography were obtained by certified photographers at baseline, Year 1, and Year 2. Certified technicians obtained OCT images from the study eye patients assigned to PRN treatment every 4 weeks and of all participants at baseline, weeks 4, 8, 12, 24, 52 (Year 1), 76, and 104 (Year 2). All the OCT images taken from the 1st year were time-domain OCT, whereas approximately 23% of OCT images in the 2nd year were spectral domain OCT.[6] Both photographic and OCT images were evaluated at the associated CATT reading centers using standardized protocols. Details regarding study-site image acquisition and reading-center grading have been previously described.[13,14]

At baseline and follow-up at weeks 4, 12, 24, 36, 52 (Year 1), 64, 76, 88, and 104 (Year 2), certified visual acuity examiners, masked to the treatment assignment, measured visual acuity after refraction in both eyes using the Electronic Visual Acuity Tester following the protocol used in the Diabetic Retinopathy Clinical Research Network.[15] The visual acuity was also measured, but without refraction, at other follow-up visits, which occurred every 4 weeks after enrollment. The visual acuity scores from the Electronic Visual Acuity

Tester range from 0 to 100, corresponding to Snellen equivalents of worse than 20/800 to 20/10. At baseline and follow-up visits, the participants were interviewed by the study coordinator about the dose, frequency, and the dates of use of all systemic and topical medications, including IOP-lowering medications.

### *Statistical Analyses*

The medication logs of all study participants were reviewed for concurrent use of IOP-lowering agents, which were subclassified based on the underlying mechanism of action: increased outflow of aqueous humor (Group A) or decreased aqueous humor production (Group B) (Table 1). For inclusion into either group, only eyes continuously receiving the corresponding medication for the entire 2-year treatment period were considered. To independently assess the effect of IOP-lowering agents in each group, any eyes using mixed-mechanism drugs (i.e., brimonidine) or medications from more than one group (i.e., Group A and B) were excluded from analysis. The control group included all patients who never took any IOP-lowering agents during the 2 years. A flow diagram of the study design is detailed in Figure 1.

Functional and anatomic outcomes at years 1 and 2 in each IOP-lowering group were compared with the control group using 2-sample *t*-test or Wilcoxon rank sum test for continuous outcomes and Fisher's exact test for categorical outcomes. For the comparison of visual acuity and thickness between Groups A and B versus controls, we also performed the multivariate analysis that adjusted by their baseline value, anti-VEGF treatment drug and regimen. In addition, to improve the statistical power for the comparisons between Group A and Group B patients vs. controls, we performed longitudinal analysis for treatment responses of visual acuity and OCT thickness measures. In the longitudinal analyses, the visual acuity change from baseline at weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104 was simultaneously modeled as an outcome variable, and the predictor variables included time (as categorical variable), and the group indicator, their baseline value, anti-VEGF drug, and regimen received in CATT. The linear mixed-effect model was used to account for the correlations from longitudinal visual acuity measures.[16,17] Similar longitudinal analyses were performed for change in OCT thickness from baseline at weeks 4, 8, 12, 24, 52, 76, and 104.

Data for continuous variables were recorded as mean ± standard error (SE) unless otherwise specified. Statistical analyses were performed using SAS software version 9.4 (SAS Inc, Cary, NC), and 2-sided *P* values less than 0.05 were considered to be statistically significant.

Table 1. The Frequency of IOP-Lowering Medications Use Used in Group A and Group B Patients

| Glaucoma Drugs | Used Throughout 2 Years<br>Patient (%)* |
|---|---|
| Group A: increases aqueous outflow | 28 (2.4) |
| Pilocarpine | 0 (0) |
| Bimatoprost | 5 (0) |
| Latanoprost | 18 (1.5) |
| Travoprost | 13 (1.1) |
| Group B: aqueous suppressant | 19 (1.6) |
| Betaxolol | 1 (0) |
| Levobunolol | 1 (0) |
| Timolol maleate | 10 (0.8) |
| Dorzolamide HCL/timolol maleate | 8 (0.7) |
| Dorzolamide HCL | 2 (0) |
| Brinzolamide | 2 (0) |
| Acetazolamide | 1 (0) |

*Some patients used more than one IOP-lower medications of the same group.
DA, disk area; HCL, hydrochloride.

## Results

Inclusion criteria were met in 28 patients who took IOP-lowering agents that increased aqueous outflow (Group A) for 2 years and 19 patients who took IOP-lowering agents that decreased aqueous production (Group B) for 2 years, whereas 857 patients who never took IOP-lowering medications served as controls. Baseline characteristics of the three groups are outlined in Table 2. Compared with controls, Group A patients had a higher proportion with hypertension (89.3 vs. 67.7%, $P = 0.02$) and a lower proportion with vitreomacular traction (0 vs. 14.0%, $P = 0.04$). No significant differences in baseline characteristics were found between Group B patients and controls. Both groups had baseline visual acuity similar to controls ($P > 0.20$). Both groups also had similar distributions of anti-VEGF treatment drug and dosing regimen as controls ($P > 0.50$, Table 2).

### *Visual and Anatomical Outcomes*

After 2 years, mean (±SE) visual acuity improved +6.3 ± 0.6 letters from baseline in the control group compared with +3.5 ± 3.9 letters gain in Group A ($P = 0.38$) and +13.8 ± 2.7 letters gain in Group B ($P = 0.052$, Table 3). The proportion of ≥3-line gainers at 2 years was 29.4% in the control group, 28.6% in Group A ($P = 0.92$ vs. controls), and 47.4% in Group B ($P = 0.09$ vs. controls, Table 3). After adjustment by their baseline values, anti-VEGF treatment drug, and regimen, Group B had 6 more letters in visual acuity gain (95% confidence interval: −0.9 to 13.6 letters, $P = 0.09$) compared with the control group (Table 4).

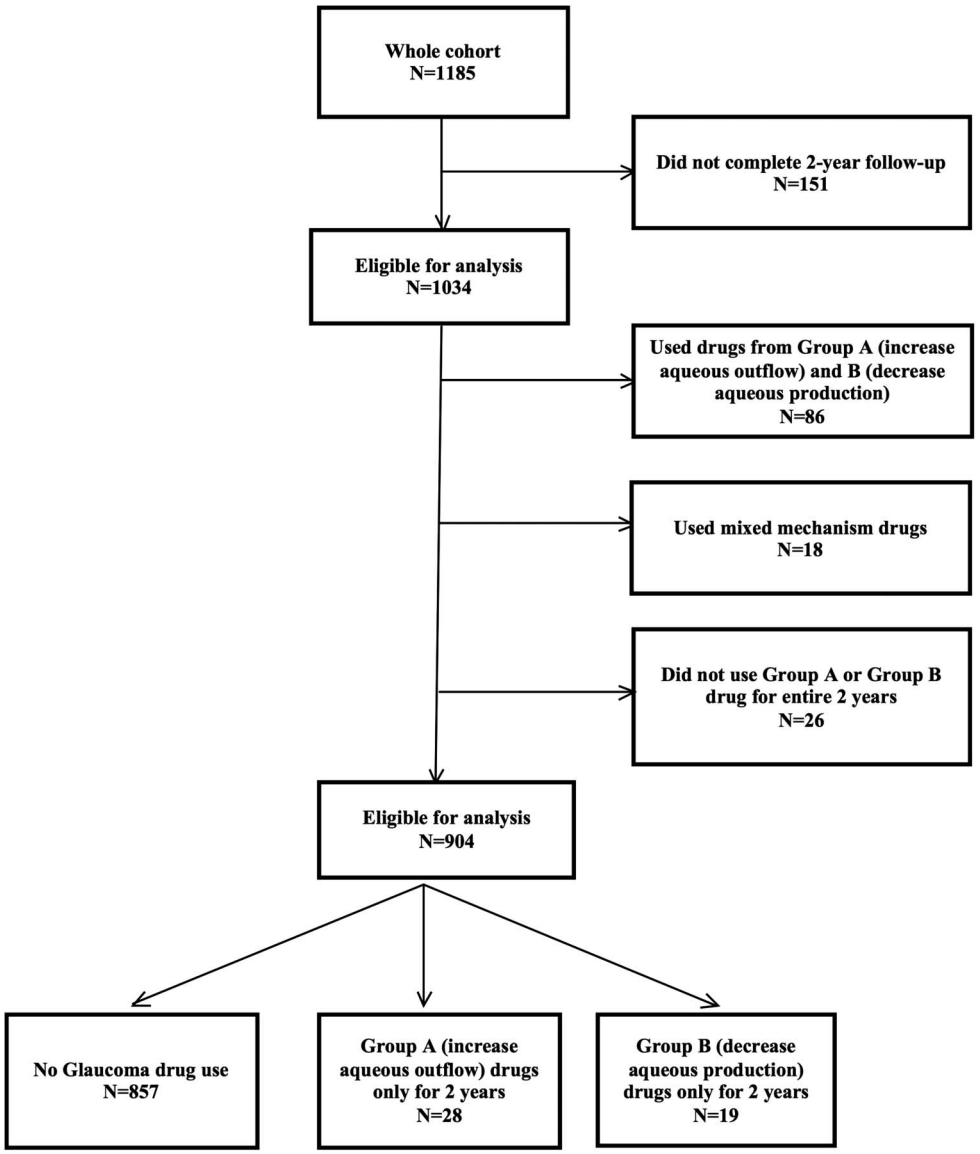


**Fig. 1.** Flowchart for study inclusion.

Mean change in retinal thickness from baseline to Year 2 in the control group was −54.9 μm, compared with −80.6 μm in Group A ($P$ = 0.26) and −96.8 μm in Group B ($P$ = 0.13, Table 3). Mean change in total thickness from baseline in the control group was −162.5 μm, compared with −179.8 μm in Group A ($P$ = 0.63) and −238.2 μm in Group B ($P$ = 0.08) after 2 years of therapy. After adjustment by their baseline value, anti-VEGF treatment drug, and regimen, Group B's total thickness decreased 40 μm more (95% confidence interval: −99 to 19 μm, $P$ = 0.19) compared with control group (Table 4).

Similar functional and anatomical responses after 1 year of therapy are further outlined in a **Supplemental Digital Content 1** (see **Table**, http://links.lww.com/IAE/A827).

*Number of Injections in pro re nata Groups*

The mean number of intravitreal anti-VEGF injections administered through 2 years in the PRN arms (either PRN through 2 years or monthly in Year 1 switched over to PRN in Year 2) was 15.7 in the control group, 16.7 in Group A ($P$ = 0.50 vs. controls), and 13.9 in Group B ($P$ = 0.39 vs. controls, Table 3).

*Longitudinal Analysis*

In multivariate longitudinal analysis (Table 4), the visual acuity change from baseline over 2 years was +6.8 letters in controls, +3.9 letters in Group A, and +9.4 letters in Group B ($P$ = 0.39, Figure 2). The corresponding mean retinal thickness change from

Table 2. Comparisons of Baseline Characteristics of Patients in IOP-Lowering Medication Groups Versus Controls

| Baseline Characteristics | Controls: Without Using Any IOP-Lowering Medications (N = 857) | Group A (Increased Aqueous Outflow) Users (N = 28) | *P* for Group a vs. Controls | Group B (Aqueous Suppressant) Users (N = 19) | *P* for Group B vs. Controls |
|---|---|---|---|---|---|
| Age (years): mean (SE) | 78.6 (7.6) | 80.6 (7.2) | 0.18 | 80.6 (6.6) | 0.25 |
| Sex: male (%) | 315 (36.8) | 7 (25.0) | 0.20 | 7 (36.8) | 0.99 |
| Hypertension (%) | 580 (67.7) | 25 (89.3) | 0.02 | 14 (73.7) | 0.58 |
| Diabetes (%) | 147 (17.2) | 4 (14.3) | 0.69 | 4 (21.1) | 0.66 |
| Current smoking (%) | 74 (8.6) | 2 (7.1) | 0.55 | 0 (0.0) | 0.36 |
| Baseline VA: mean (SE) | 61.3 (13.3) | 59.1 (16.2) | 0.40 | 57.4 (14.9) | 0.21 |
| Total area of CNV lesion: mean (SE) | 2.5 (2.5) | 2.6 (2.2) | 0.75 | 2.5 (2.2) | 0.96 |
| Type of CNV (%) | | | 0.38 | | 0.29 |
| Classic only | 174 (20.3) | 9 (32.1) | | 6 (31.6) | |
| Occult only | 518 (60.4) | 15 (53.6) | | 11 (57.9) | |
| Mixed | 148 (17.3) | 3 (10.7) | | 1 (5.3) | |
| Unknown | 17 (2.0) | 1 (3.6) | | 1 (5.3) | |
| Hemorrhage (associated with the lesion) | | | 0.38 | | 0.56 |
| None | 320 (37.3%) | 12 (42.9%) | | 7 (36.8%) | |
| <=1 DA | 444 (51.8%) | 11 (39.3%) | | 8 (42.1%) | |
| >1, <=2 DA | 42 (4.9%) | 1 (3.6%) | | 2 (10.5%) | |
| >2 DA | 37 (4.3%) | 3 (10.7%) | | 1 (5.3%) | |
| Unknown | 14 (1.6%) | 1 (3.6%) | | 1 (5.3%) | |
| Presence of GA (%) | 55 (6.4) | 2 (7.1) | 0.88 | 1 (5.3) | 0.84 |
| Retinal thickness ($\mu$m): mean (SE) | 214.0 (100.0) | 223.6 (122.2) | 0.62 | 246.5 (128.2) | 0.16 |
| Total thickness ($\mu$m): mean (SE) | 462.5 (188.0) | 463.9 (187.9) | 0.97 | 513.4 (197.8) | 0.24 |
| Intraretinal fluid (%) | 632 (75.0) | 24 (85.7) | 0.19 | 16 (84.2) | 0.36 |
| SRF (%) | 719 (84.4) | 21 (75.0) | 0.18 | 16 (84.2) | 0.98 |
| Sub-RPE fluid (%) | 431 (54.5) | 14 (53.8) | 0.95 | 9 (50.0) | 0.71 |
| RPE elevation maximum height ($\mu$m): median (1st quartile, 3rd quartile) | 121 (66, 264) | 154 (44, 242) | 0.91 | 132 (66, 286) | 0.99 |
| VMT-vitreous attached within central 3 mm (%) | 113 (14.0) | 0 (0.0) | 0.04 | 1 (5.3) | 0.28 |
| Drug group (%) | | | 0.96 | | 0.79 |
| Ranibizumab | 433 (50.5) | 14 (50.0) | | 9 (47.4) | |
| Bevacizumab | 424 (49.5) | 14 (50.0) | | 10 (52.6) | |
| Regimen group (%) | | | 0.67 | | 0.52 |
| PRN | 433 (50.5) | 13 (46.4) | | 12 (63.2) | |
| Switched | 212 (24.7) | 6 (21.4) | | 3 (15.8) | |
| Monthly | 212 (24.7) | 9 (32.1) | | 4 (21.1) | |

GA, geographic atrophy; VA, visual acuity; VMT, vitreomacular traction.

baseline was −53.5 $\mu$m in controls vs. −62.2 $\mu$m in Group A vs. −71.4 $\mu$m in Group B ($P$ = 0.06, Figure 3), and mean total thickness change from baseline was −156.6 $\mu$m vs. −167.2 $\mu$m vs. −211.3 $\mu$m in each of the 3 groups, respectively ($P$ = 0.03, Figure 4).

## Discussion

Motivated by findings from a previous pilot study which suggested that topical aqueous suppressants (dorzolamide–timolol) in combination with anti-VEGF injections might help improve anatomical

Table 3. Comparisons of visual acuity Outcomes and Morphological Outcomes at Year 2 of IOP-Lowering Medication Groups versus Controls

| Outcomes at Year 2 | None (N = 857) | Group a Drugs (N = 28) | Group a vs. Control | | Group B Drugs (N = 19) | Group B vs. Control | |
|---|---|---|---|---|---|---|---|
| | | | Difference (95% CI) | *P* for Group a vs. None | | Difference (95% CI) | *P* |
| VA (letters): mean (SE) | 67.6 (18.3) | 62.6 (23.6) | −5.0 (−12.0 to 2.0) | 0.16 | 71.2 (12.4) | 3.6 (−4.7 to 11.9) | 0.39 |
| VA change from baseline (letters): mean (SE) | 6.3 (16.6) | 3.5 (20.8) | −2.8 (−9.1 to 3.4) | 0.38 | 13.8 (11.7) | 7.4 (−0.0 to 14.9) | 0.052 |
| >=15 letters decrease from baseline (%) | 77 (9.0) | 5 (17.9) | 8.9 (−2.4 to 28.7) | 0.11 | 0 (0.0) | −9.0 (−11.2 to 12.0) | 0.17 |
| >=15 letters gain from baseline (%) | 252 (29.4) | 8 (28.6) | −0.8 (−15.8 to 19.7) | 0.92 | 9 (47.4) | 18.0 (−4.4 to 41.3) | 0.09 |
| Retinal thickness ($\mu$m): mean (SE) | 159.1 (72.2) | 143.0 (67.9) | −16.1 (−43.2 to 11.0) | 0.25 | 149.8 (58.4) | −9.4 (−42.0 to 23.3) | 0.57 |
| Retinal thickness change from baseline ($\mu$m): mean (SE) | −54.9 (118.5) | −80.6 (129.2) | −25.7 (−70.4 to 19.0) | 0.26 | −96.8 (140.2) | −41.9 (−95.9 to 12.2) | 0.13 |
| SRF thickness ($\mu$m): mean (SE) | 9.4 (34.4) | 0.4 (2.1) | −9.0 (−21.7 to 3.7) | 0.17 | 15.2 (42.8) | 5.8 (−9.9 to 21.5) | 0.47 |
| Sub-RPE thickness ($\mu$m): mean (SE) | 129.7 (106.9) | 140.7 (97.8) | 11.0 (−29.1 to 51.1) | 0.59 | 110.3 (80.6) | −19.4 (−67.8 to 28.9) | 0.43 |
| Total thickness ($\mu$m): mean (SE) | 298.1 (141.0) | 284.1 (126.7) | −13.9 (−66.8 to 38.9) | 0.61 | 275.3 (103.4) | −22.8 (−86.5 to 41.0) | 0.48 |
| Change in total thickness from baseline ($\mu$m): mean (SE) | −162.5 (185.9) | −179.8 (205.9) | −17.3 (−87.5 to 52.8) | 0.63 | −238.2 (208.5) | −75.7 (−160.4 to 9.0) | 0.08 |
| Intraretinal fluid (%) | 450 (54.3) | 13 (48.1) | −6.2 (−25.5 to 13.6) | 0.52 | 8 (42.1) | −12.2 (−33.5 to 11.9) | 0.29 |
| SRF (%) | 295 (36.3) | 12 (44.4) | 8.2 (−10.6 to 28.3) | 0.39 | 7 (36.8) | 0.6 (−19.4 to 25.3) | 0.96 |
| Sub-RPE fluid (%) | 306 (38.3) | 10 (38.5) | 0.2 (−17.7 to 21.2) | 0.99 | 6 (33.3) | −5.0 (−24.3 to 20.8) | 0.67 |
| No fluid on OCT (%) | 187 (22.1) | 8 (28.6) | 6.5 (−8.4 to 27.0) | 0.41 | 6 (31.6) | 9.5 (−8.7 to 34.6) | 0.32 |

Table 3. (*Continued*)

| Outcomes at Year 2 | None (N = 857) | Group a Drugs (N = 28) | Group a vs. Control | | Group B Drugs (N = 19) | Group B vs. Control | |
|---|---|---|---|---|---|---|---|
| | | | Difference (95% CI) | *P* for Group a vs. None | | Difference (95% CI) | *P* |
| Leakage on FA (%) | 228 (27.7) | 7 (25.0) | −2.7 (−16.6 to 17.8) | 0.76 | 6 (33.3) | 5.7 (−13.6 to 31.4) | 0.60 |
| GA (%) | 200 (23.3) | 8 (28.6) | 5.2 (−9.7 to 25.7) | 0.52 | 7 (36.8) | 13.5 (−6.3 to 38.2) | 0.17 |
| Scar (%) | 362 (43.3) | 12 (42.9) | −0.4 (−18.6 to 19.6) | 0.96 | 8 (44.4) | 1.1 (−21.2 to 25.6) | 0.92 |
| Subretinal hyperreflective material (%) | 397 (47.5) | 16 (61.5) | 14.0 (−7.1 to 31.9) | 0.16 | 9 (47.4) | −0.2 (−22.6 to 23.2) | 0.99 |
| RPE elevation (%) | 799 (95.3) | 24 (85.7) | −9.6 (−29.0 to 0.1) | 0.02 | 15 (83.3) | −12.0 (−37.6 to 0.4) | 0.02 |
| RPE elevation maximum height (mm): mean (SE) | 541.2 (1,276.6) | 373.3 (1,271.7) | −168.0 (−648.2 to 312.3) | 0.49 | 641.1 (1821.7) | 99.8 (−501.9 to 701.5) | 0.75 |
| Change from baseline in RPE elevation maximum height (mm): mean (SE) | 363.3 (1,274.5) | 228.5 (1,330.3) | −134.8 (−642.3 to 372.6) | 0.60 | 459.6 (1806.1) | 96.2 (−504.7 to 697.2) | 0.75 |
| RPE elevation maximum width (mm): mean (SE) | 10,876.8 (31,175.4) | 1,420.5 (1,358.1) | −9,456.3 (−21,208.3 to 2,295.6) | 0.12 | 10,312.0 (33,262.2) | −564.8 (−15137.0 to 14,007.4) | 0.94 |
| Change from baseline in RPE elevation maximum width (mm): mean (SE) | 8,871.5 (29,824.7) | −51.1 (1,044.5) | −8,922.6 (−21103.3 to 3,258.0) | 0.15 | 8,658.4 (33,159.2) | −213.2 (−14179.1 to 13,752.7) | 0.98 |
| VMT-vitreous attached within central 3 mm (%) | 74 (9.3) | 0 (0.0) | −9.3 (−11.5 to 7.4) | 0.11 | 1 (5.6) | −3.7 (−9.4 to 20.2) | 0.59 |
| Epiretinal membrane (%) | 258 (31.6) | 13 (50.0) | 18.4 (−1.5 to 38.3) | 0.048 | 7 (36.8) | 5.3 (−14.6 to 30.0) | 0.63 |
| Mean number of injections in 2 years, PRN or switched (SE) | 15.7 (7.0) | 16.7 (5.4) | 1.0 (−1.9 to 4.0) | 0.50 | 13.9 (8.4) | −1.7 (−5.7 to 2.3) | 0.39 |

CI, confidence interval; FA, fluorescein angiography; GA, geographic atrophy; VA, visual acuity; VMT, vitreomacular traction.

Table 4. Adjusted Analysis for the Comparison of visual acuity and Morphological Outcomes

| Outcomes at Year 1 | None (N = 857) | Group a Drugs (N = 28) | Group a vs. Control | | Group B Drugs (N = 19) | Group B vs. Control | |
|---|---|---|---|---|---|---|---|
| | | | Difference (95% CI) | *P* for Group a vs. None | | Difference (95% CI) | *P* |
| Outcomes at Year 1: mean (SE) | | | | | | | |
| VA change from baseline (letters) | 7.8 (0.5) | 5.6 (2.7) | −2.2 (−7.5 to 3.2) | 0.42 | 10.2 (3.3) | 2.4 (−4.0 to 8.9) | 0.46 |
| Retinal thickness change from baseline ($\mu$m) | −57.7 (2.0) | −78.2 (11.2) | −20.4 (−42.7 to 1.8) | 0.07 | −68.7 (13.6) | −11.0 (−38.0 to 15.9) | 0.42 |
| Change in total thickness from baseline ($\mu$m) | −168.0 (4.2) | −201.7 (23.2) | −33.8 (−80.0 to 12.4) | 0.15 | −216.6 (28.2) | −48.7 (−104.6 to 7.2) | 0.09 |
| Outcomes at Year 2: mean (SE) | | | | | | | |
| VA change from baseline (letters) | 6.4 (0.5) | 2.8 (3.0) | −3.6 (−9.7 to 2.4) | 0.24 | 12.8 (3.7) | 6.4 (−0.9 to 13.6) | 0.09 |
| Retinal thickness change from baseline ($\mu$m) | −55.8 (2.5) | −72.3 (13.5) | −16.5 (−43.4 to 10.4) | 0.23 | −67.6 (16.4) | −11.7 (−44.2 to 20.8) | 0.48 |
| Change in total thickness from baseline ($\mu$m) | −163.3 (4.5) | −176.9 (24.5) | −13.5 (−62.4 to 35.3) | 0.59 | −203.2 (29.8) | −39.8 (−98.9 to 19.3) | 0.19 |
| Longitudinal analysis over 2 years: mean (SE) | | | | | | | |
| VA change from baseline (letters) | 6.8 (0.4) | 3.9 (2.5) | −2.9 (−7.8 to 2.1) | 0.26 | 9.4 (3.0) | 2.6 (−3.4 to 8.5) | 0.39 |
| Retinal thickness change from baseline ($\mu$m) | −53.5 (1.6) | −62.2 (10.0) | −8.7 (−28.7 to 11.3) | 0.39 | −71.4 (9.3) | −17.9 (−36.5 to 0.7) | 0.06 |
| Change in total thickness from baseline ($\mu$m) | −156.6 (3.6) | −167.2 (18.8) | −10.5 (−48.0 to 27.0) | 0.58 | −211.3 (24.3) | −54.7 (−103.2 to −6.2) | 0.03 |

CI, confidence interval; VA, visual acuity.

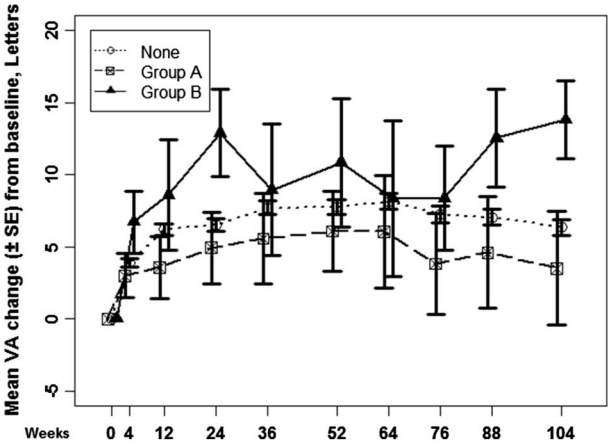


**Fig. 2.** Mean visual acuity change from baseline (±SE) over time for patients in groups A, B, and matched controls. VA, visual acuity.

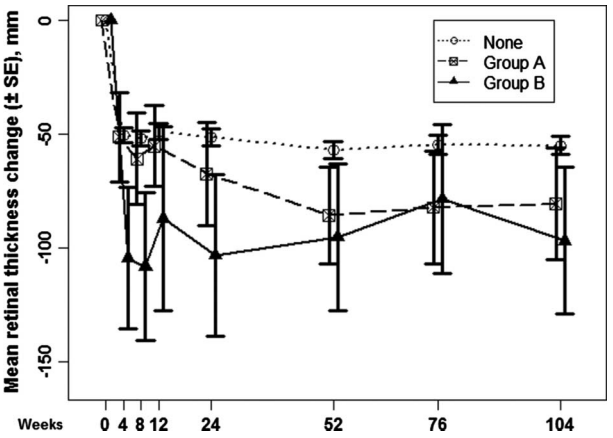


**Fig. 3.** Mean retinal thickness change from baseline (±SE) over time for patients in groups A, B, and matched controls.

outcomes,[12] we evaluated the impact of concurrent use of IOP-lowering medication on treatment outcomes among CATT patients treated with ranibizumab or bevacizumab on a monthly or PRN basis for neovascular AMD. The findings from this secondary data analysis may suggest a potential added anatomical and functional benefit from aqueous suppressants, but not agents that increase aqueous outflow, over 2 years of anti-VEGF therapy. Because the number of CATT participants taking aqueous suppressants for 2 years was small, these findings must be cautiously interpreted and perhaps serve as a basis for future prospective studies.

Any potential benefit of Group B agents on neovascular AMD treatment outcomes in CATT may be multifactorial. Most notably, by decreasing aqueous humor production by up to 50%,[18] the outflow of fluid may be subsequently hindered, thereby prolonging the half-life of any intraocular VEGF inhibitor present. Although the exact mechanism by which intravitreal anti-VEGF agents are cleared is not completely understood, there is evidence that passage through the anterior chamber may play a role.[8–11] Gaudreault et al previously demonstrated that concentrations of ranibizumab in the aqueous humor after a single intravitreal injection, although much lower than in the vitreous, seem to decline in parallel with vitreous levels.[11] Two small, prospective studies evaluating the use of topical dorzolamide–timolol support this mechanism. In the first, Byeon et al demonstrated that in patients receiving a single intravitreal bevacizumab injection for the treatment of macular edema secondary to branch or central retinal vein occlusion, the mean central subfield thickness was significantly lower after 5 weeks in eyes randomly assigned to receive topical dorzolamide–timolol drops compared with controls (no drops, $P = 0.03$). However, by 9 weeks, there was no longer a difference between the 2 groups, leading the authors to conclude that aqueous suppression may have delayed the clearance of bevacizumab.[9] In the second study, Sridhar et al selected patients with persistent exudation due to neovascular AMD despite chronic, fixed-interval anti-VEGF therapy. These patients were maintained on the same anti-VEGF medication and interval between injections; the only difference was the addition of topical dorzolamide–timolol.[12] Ten eyes of 10 patients completed the study protocol, and showed statistically significant reductions in mean central subfield thickness as well as maximum SRF height measurements at each of the 4 study visit time points. However, visual acuity did not improve significantly, which may have been due to either chronic exudation before addition of the drops or the relatively short study duration. It was proposed that if topical dorzolamide–timolol is given earlier in the course of anti-VEGF treatment for incomplete responders rather than for chronic, refractory disease, more functional benefit may be achieved. This seems

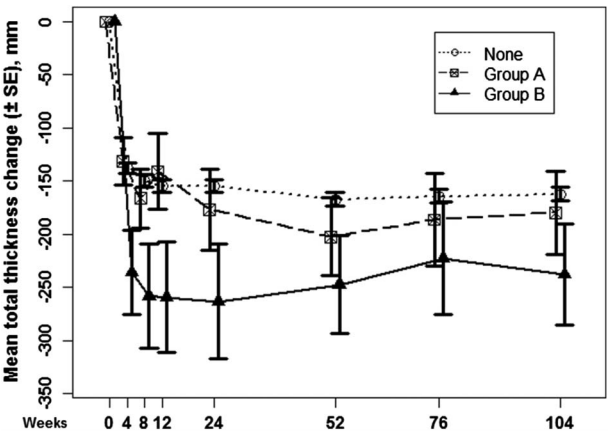


**Fig. 4.** Mean total thickness change from baseline (±SE) over time for patients in groups A, B, and matched controls.

to be corroborated by the current study's findings of significant visual acuity gains in patients on concurrent aqueous suppression therapy during the initial 2 years of anti-VEGF treatment.

In addition to decreasing aqueous humor production, Group B agents (i.e., beta blockers or carbonic anhydrase inhibitors) may have had direct retinal effects, which contributed to the observed outcomes in this study. Previous investigations in a mouse model of oxygen-induced retinopathy have demonstrated that beta-adrenergic blockade reduced upregulation of the VEGF cascade and other proangiogenic factors while decreasing hypoxic retinopathy and retinal neovascularization.[19–21] A separate mouse model of laser-induced CNV further showed that beta-adrenergic blockade attenuated CNV formation and reduced VEGF expression.[22] Studies in humans investigating the effects of systemic beta-adrenergic blockade have thus far yielded conflicting results. A retrospective case series of 46 patients with neovascular AMD found that patients receiving oral beta blockers (n = 18) were statistically more likely to receive fewer intravitreal injections of bevacizumab than their counterparts not taking the class of medication.[23] However, this positive effect was not corroborated by a recent study evaluating a large national insurance claims database, which found that use of oral beta blockers (n = 239 patients) was not associated with a decreased number of intravitreal injections for individuals with neovascular AMD compared with those taking oral calcium channel blockers (n = 155 patients).[24] Furthermore, findings from the Beaver Dam Eye Study revealed that oral beta blockers were associated with a 71% increased hazard of incident neovascular AMD.[25] Additionally, a separate retrospective series comparing 250 patients with neovascular AMD to 250 non-neovascular AMD controls demonstrated no difference in the rate of beta blocker usage between both groups, arguing against a protective effect from this class of medication in preventing CNV.[26] Whether administration of topical beta blockers may confer an added benefit by delivering greater concentrations of medication to the target tissue remains to be determined.

Dorzolamide, a carbonic anhydrase inhibitor, has been used topically with some success to treat macular edema secondary to various conditions, including retinitis pigmentosa,[27,28] X-linked retinoschisis,[29] choroideremia,[30] and systemic taxane therapy.[31,32] Inhibition of Müller and RPE cell carbonic anhydrase may modulate Müller cell activity and RPE pump function, respectively, resulting in enhanced transfer of intraretinal and SRF to the choroid, thereby improving macular edema.[33,34] In addition, topical dorzolamide may positively influence the local retinal microcirculation[35,36] and improve choroidal perfusion as demonstrated in a placebo-controlled study of 36 patients with non-neovascular AMD.[37]

If aqueous suppressants prolong the effect of intraocular VEGF inhibition, one may reasonably expect that eyes in CATT not receiving regular monthly injections (i.e., PRN through 2 years or monthly in Year 1 switched over to PRN in Year 2) would require fewer injections while on aqueous suppressants than controls. Although Group B required nominally fewer injections (13.9) after 2 years compared with controls (15.7), this difference was not statistically significant. That Group A required the greatest number of injections (16.7) during the study period, however, may further implicate aqueous humor outflow through the anterior chamber in the clearance of VEGF inhibitors from the eye because medications that facilitate this pathway may increase medication clearance and shorten the effect duration. These findings suggest that, in the very least, patients with neovascular AMD requiring glaucoma therapy may benefit more from aqueous suppressant treatment than from drug therapy that increases aqueous outflow. Additional larger studies will be required to confirm this hypothesis.

There are several limitations to this secondary data analysis, including its retrospective nature and the relatively small sample size of patients taking only one class of IOP-lowering medications continuously during the study period. Although we did not observe significant baseline differences in Group A and Group B patients compared with controls, the power for these comparisons is low due to limited sample sizes in each group; thus, the absence of a significant difference is not necessarily evidence of absence of a meaningful difference. Although we made numerous statistical comparisons for various morphological and functional outcomes, no corrections were made for multiple comparisons. Additionally, we are not able to determine whether the beneficial effect we observed from Group B medications can be generalized to this class or whether it is directly attributable to a specific agent. Furthermore, we cannot exclude the potential confounding effect of underlying glaucoma to the visual outcomes observed in either Group A or B. Finally, patient compliance among those using IOP-lowering medications was dependent on self-reporting during CATT. However, a major strength of this study is that it included only eyes that were given IOP-lowering medication continuously throughout the entire 2-year period, and excluded those taking multiple medications from different classes so that we could assess drug effect not confounded by mixed drug classes.

In summary, concurrent use of aqueous suppressants during intravitreal anti-VEGF treatment for neovascular AMD may suggest a trend toward improved visual outcomes and possibly with greater reductions in retinal thickness and total thickness after 2 years in a secondary analysis of CATT data. A similar effect, however, was not observed to the same extent with agents that reduce IOP through increasing aqueous outflow. Because of the small sample size and the nature of secondary data analysis, these findings must be interpreted with caution. However, if these results are consistent in future prospective randomized studies and/or secondary analyses of other similar clinical trials, combination therapy with aqueous suppressants in addition to anti-VEGF injections may improve outcomes in the treatment of neovascular AMD.

**Key words:** age-related macular degeneration, aqueous outflow, beta blockers, carbonic anhydrase inhibitors, choroidal neovascularization, dorzolamide, intraocular pressure, timolol.

## References

1. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
2. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355: 1432–1444.
3. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2005;36:331–335.
4. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363–372.
5. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–1908.
6. CATT Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: 2-year results. Ophthalmology 2012;119:1388–1398.
7. Heir JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119: 2537–2548.
8. Byeon SH, Kwon OW, Song JH, et al. Prolongation of activity of single intravitreal bevacizumab by adjuvant topical aqueous depressant (timolol-dorzolamide). Graefes Arch Clin Exp Ophthalmol 2009;247:35–42.
9. Bakri SJ, Snyder MR, Reid JM, et al. Pharmacokinetics of intravitreal bevacizumab (Avastin). Ophthalmology 2007; 114:855–859.
10. Stewart MW. Predicted biologic activity of intravitreal bevacizumab. Retina 2007;27:1196–1200.
11. Gaudreault J, Fei D, Rusit J, et al. Preclinical pharmacokinetics of ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci 2005;46: 726–733.
12. Sridhar J, Hsu J, Shahlaee A, et al. Topical dorzolamide-timolol with intravitreous anti-vascular endothelial growth factor for neovascular age-related macular degeneration. JAMA Ophthalmol 2016;134:437–443.
13. Grunwald JE, Daniel E, Ying GS, et al; CATT Research Group. Photographic assessment of baseline fundus morphologic features in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2012;119: 1634–1641.
14. DeCroos FC, Toth CA, Stinnett SS, et al; CATT Research Group. Optical coherence tomography grading reproducibility during the comparison of age-related macular degeneration treatments trials. Ophthalmology 2012;119: 2549–2557.
15. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. Am J Ophthalmol 2003;135:194–205.
16. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963–974.
17. Ying GS, Maguire MG, Glynn R, Rosner B. Tutorial on biostatistics: linear regression analysis of continuous correlated eye data. Ophthalmic Epidemiol 2017;24:130–140.
18. Brubaker RF, Ingram CJ, Schoff EO, Nau CB. Comparison of the efficacy of betaxolol-brinzolamide and timolol-dorzolamide as suppressors of aqueous humor flow in human subjects. Ophthalmology 2000;107:283–287.
19. Ristori C, Filippi L, Dal Monte M, et al. Role of the adrenergic system in a mouse model of oxygen-induced retinopathy: antiangiogenic effects of β-adrenoreceptor blockade. Invest Ophthalmol Vis Sci 2011;52:155–170.
20. Martini D, Monte MD, Ristori C, et al. Antiangiogenic effects of $\beta_2$-adrenergic receptor blockade in a mouse model of oxygen-induced retinopathy. J Neurochem 2011;119: 1317–1329.
21. Casini G, Dal Monte M, Fornaciari I, et al. The β-adrenergic system as a possible new target for pharmacologic treatment of neovascular retinal diseases. Prog Retin Eye Res 2014;42: 103–129.
22. Lavine JA, Sang Y, Wang S, et al. Attenuation of choroidal neovascularization by $\beta_2$-adrenoreceptor antagonism. JAMA Ophthalmol 2013;131:376–382.
23. Montero JA, Ruiz-Moreno JM, Sanchis-Merino E, Perez-Martin S. Systemic β-blockers may reduce the need for repeated intravitreal injections in patients with wet age-related macular degeneration treated by bevacizumab. Retina 2013;33:508–512.
24. Traband A, Shaffer JA, VanderBeek BL. Systemic beta blockers in neovascular age-related macular degeneration. Retina 2017;37:41–46.
25. Klein R, Myers CE, Klein BE. Vasodilators, blood pressure-lowering medications, and age-related macular degeneration: the Beaver Dam Eye Study. Ophthalmology 2014;121: 1604–1611.
26. Thomas AS, Redd T, Hwang T. Effect of systemic β-blockers, ACE inhibitors, and angiotensin receptor blockers on development of choroidal neovascularization in patients with age-related macular degeneration. Retina 2015;35:1964–1968.
27. Grover S, Apushkin MA, Fishman GA. Topical dorzolamide for the treatment of cystoid macular edema in patients with retinitis pigmentosa. Am J Ophthalmol 2006;141: 850–858.

28. Ikeda Y, Hisatomi T, Yoshida N, et al. The clinical efficacy of a topical dorzolamide in the management of cystoid macular edema in patients with retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol 2012;250:809–814.
29. Genead MA, Fishman GA, Walia S. Efficacy of sustained topical dorzolamide therapy for cystic macular lesions in patients with X-linked retinoschisis. Arch Ophthalmol 2010;128:190–197.
30. Genead MA, McAnany JJ, Fishman GA. Topical dorzolamide for treatment of cystoid macular edema in patients with choroideremia. Retina 2012;32:826–833.
31. Ehlers JP, Rayess H, Steinle N. Topical dorzolamide therapy for taxane-related macular oedema. Eye (Lond) 2013;27: 102–104.
32. Dwivedi R, Tiroumal S. Possible efficacy of topical dorzolamide in the treatment of paclitaxel-related cystoid macular edema. Retin Cases Brief Rep 2016;12:75–79.
33. Terashima H, Suzuki K, Kato K, Sugai N. Membrane-bound carbonic anhydrase activity in the rat corneal endothelium and retina. Jpn J Ophthalmol 1996;40:142–153.
34. Adijanto J, Banzon T, Jalickee S, et al. $CO_2$-induced ion and fluid transport in human retinal pigment epithelium. J Gen Physiol 2009;133:603–622.
35. Harris A, Arend O, Arend S, Martin B. Effects of topical dorzolamide on retinal and retrobulbar hemodynamics. Acta Ophthalmol Scand 1996;74:569–572.
36. Harris A, Jonescu-Cuypers CP, Kagemann L, et al. Effect of dorzolamide timolol combination versus timolol 0.5% on ocular bloodflow in patients with primary open-angle glaucoma. Am J Ophthalmol 2001;132:490–495.
37. Harris A, Ciulla TA, Pratt LM, et al. The effects of dorzolamide on choroidal and retinal perfusion in non-exudative age related macular degeneration. Br J Ophthalmol 2003;87:753–757.