The use of dorzolamide versus other hypotensive agents to prevent glaucomatous progression

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Purpose: To evaluate progression rates with dorzolamide compared with other hypotensive agents in primary open-angle glaucoma.

Methods: Patients who were treated over 5 years with dorzolamide versus other hypotensive agents were reviewed. The groups were matched by intraocular pressure, cardiovascular history, and age.

Results: In 50 matched pairs, 2 (4%) of dorzolamide and 7 (14%) of control patients suffered glaucomatous progression (p = 0.09). Progressed dorzolamide patients had pressures of 13 versus 15–20 mmHg in the control group. Control patients progressed after 26.4 months and dorzolamide patients after 38.9 months.

Conclusions: Although the results were not statistically significant, this pilot trial demonstrated a trend towards less glaucomatous progression in patients treated with an assumed active blood flow product. In addition, progression was delayed and occurred at lower pressures in the active blood flow group. This pilot trial suggests that future prospective, long-term, clinical outcomes studies in patients treated with a medicine with a positive ocular blood flow effect may be warranted.

Keywords: blood flow, ocular hypotensive agents, dorzolamide, glaucomatous progression

Introduction

Much information now exists in the literature confirming that the reduction of intra-ocular pressure helps prevent, but does not absolutely preclude, progression of glaucoma (Mao et al 1991; Stewart et al 1993, 2000; AGIS Investigators 2000; Lichter et al 2001; Konstas et al 2004). Because some patients still progress despite pressure reduction, other risk factors may exist that allow some patients to progress despite treatment. However, little information is available that identifies these "other" specific risk factors that cause glaucomatous progression.

Although controversial, decreased ocular blood flow, as well as poor ocular perfusion pressure associated with reduced systemic blood pressure, have been frequently discussed as potential risk factors for the progression of glaucoma (Stewart 1998; Hayreh et al 1999). Unfortunately, little long-term information exists indicating that blood flow is a part of the pathogenesis of glaucoma or that improving blood flow provides improved clinical outcomes more than lowering the intraocular pressure in isolation (Stewart 1998). Further, several problems exist in designing a trial to determine any influence of blood flow in glaucoma, which are not limited to, but include: first, that the potential improved ocular hemodynamics from merely reducing the intraocular pressure is a confounding variable to an actual primary blood flow effect; and second, that the expense of such a study would be high because of the required long-term, double-masked, parallel, multi-center, prospective, trial design.

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An initial cost- and time-effective method for evaluating clinical outcomes from a potential increased ocular blood flow might be a retrospective review of existing patient records. In such a design a potential blood flow effect could be isolated, at least in part, by matching patients by intra-ocular pressure between groups treated with medicines that demonstrate improved ocular hemodynamics to a control that does not have a blood flow effect.

The purpose of this pilot study was to evaluate the long-term progression rates of primary open-angle glaucoma patients treated with an agent that has been shown to improve ocular hemodymanic characteristics clinically (ie, dorzolamide, active blood flow agent) versus medicines that have not shown a conclusive and consistent clinical ocular hemodynamic effect (control group, non-active blood flow agent). Patients were matched 1:1 by intraocular pressure so any differences in progression rates between groups might be potentially ascribed to non-pressure-related factors.

Materials and methods
Patients
Patients were included in this retrospective analysis who fulfilled the following conditions: $\geq$40 to $\leq$80 years of age; a clinical diagnosis of primary open-angle glaucoma in at least one eye (study eye); treated with at least 5 years follow-up from July 1997 by dorzolamide (Trusopt™, Merck & Co., Whitehouse Station, NJ, USA) (dorzolamide group: assumed active ocular blood flow agent) or ocular hypotensive agents (assumed to be both non-active blood flow agents and non-active neuroprotective agents) (Table 1).

Generally medicines were classified as non-active neuroprotective or blood flow product based on blood flow studies. We did not use animal or in vitro studies to make a clinical blood flow classification because differing medicine concentrations and availability of the active molecule to the receptors in vitro can alter results from what might be observed clinically. Consequently, based on clinical trials dorzolamide, betaxolol, and acetazolamide were classified as a blood flow product (Bonte et al 1988; Turacli et al 1998; Bernd et al 2001). Unoprostone was classified as both a neuroprotective and blood flow product (Melamed 2002). Brimonidine was classified as a neuroprotective product (Yoles et al 1999). Further, although latanoprost has been known to improve blood flow the results are inconsistent and are thought to be due to its marked reduction of intraocular pressure and not an independent effect on ocular vascularity.

Within the 5-year follow-up, patients must have been treated for 50% of the total follow-up time with the dorzolamide/timolol maleate fixed (Cosopt™, Merck & Co., Whitehouse Station, NJ) or unfixed combination and 80% of the follow-up time patients must have been treated with dorzolamide (as a single agent or as the fixed combination). However, patients may have used an assumed active blood flow or neuroprotective agent(s) for up to 25% of the follow-up period in either group (Table 1). Patients may have been treated with any number of medications or surgeries. At visit 1 patients must have had a mean intraocular pressure of $\leq$21 mmHg, have been on a stable medical regimen for at least one visit prior to visit 1, and have had a mean intraocular pressure over the follow-up period of $\geq$10 to $\leq$21 mm Hg inclusive.

Patients were excluded from the analysis who had: any abnormality preventing reliable applanation tonometry in study eye; any opacity or patient uncooperativeness that restricted adequate examination of the ocular fundus or anterior chamber in the study eye or poor follow-up (less than 8 visits over 5 years; or did not have baseline visual

Table 1 Classification of glaucoma agents and number of patients with each medicine

Name	Control	Dorzolamide	Class of agent	Allowed use
Dorzolamide	1	19	Blood flow	Study group only
DTFC	0	44	Blood flow	Study group only
Prostaglandin analogs	26	23	Non-active	Either group
Non-selective b-blockers	43	36	Non-active	Either group
Apraclonidine	1	2	Non-active	Either group
Betaxolol	1	7	Blood flow	$\leq$25% in either group
Unoprostone	1	2	Blood flow and neuroprotective	$\leq$25% in either group
Brimonidine	0	14	Neuroprotective	$\leq$25% in either group
Pilocarpine	8	7	Non-active	Either group
Systemic CAI	1	0	Blood flow	$\leq$25% in either group

Abbreviations: CAI, carbonic anhydrase inhibitors; DTFC, dorzolamide/timolol maleate fixed combination.

field and optic disc exam within 12 months before or within 6 months after visit 1.

Procedures

A HIPPA waiver was obtained for this study. Patients who met the inclusion and exclusion criteria had the following recorded: date, age, race, gender, cardiovascular history, right/left eye, and glaucoma surgical and medication history. One eye was randomly chosen to be included if both eyes qualified. The ophthalmic examinations recorded were: Goldmann applanation tonometry, Snellen visual acuity, and the most recent dilated funduscopic exam of the optic nerve and the visual field (available at Month -12 to Month -6). The visual field was performed using threshold techniques on the Humphrey Field Analyzer (Humphrey Instruments, San Leadro, CA). Glaucoma medicines were also recorded at each visit.

The matching criteria were then determined to be: the mean intraocular pressure at every visit over 5 years (± 2 mmHg), age at visit 1 (± 10 years) and the presence or absence of cardiac disease. A positive cardiac history included, but was not limited to, systemic hypertension, ischemic heart disease, angina, myocardial infarction, coronary artery bypass graft, or angioplasty. The patient records for this study were reviewed in alphabetical order in the glaucoma practice of one of the authors (DGD). Data collection was performed by the clinical glaucoma research fellow (SD) and several experienced ophthalmic research coordinators. All charts that met the inclusion and exclusion criteria were available for matching and no chart was excluded from consideration. The first appropriate match found was used for the study. The principal investigator (WCS), clinical investigator (DGD), and the lead coordinator (JAS) were masked to patient matching procedures. Once matching was complete the data were entered and analyzed by a separate team including the lead investigator (WCS).

At each interim visit up to 5 years and the exit visit the following information was collected: date, glaucoma medications and surgeries, intraocular pressure, visual acuity, and any optic disc or field exam results. If the patient was noted to progress this was noted as well and the patient was discontinued from the follow-up process. If progression occurred, the reason for progression, if available, was noted. Progression was diagnosed from the clinical interpretation on the patient's record as noted by the investigator (DGD). The clinical criteria for progression were those generally accepted in routine practice including progressive optic nerve head thinning, saucerization, or the appearance of a nerve fiber layer hemorrhage at, or close to, the optic nerve head and/or worsening or the development of visual field defect including nasal step or Seidel's, arcuate, or pericentral scotoma.

Statistics

All data analyses were two-sided and a p value of 0.05 was used to declare significance. The primary safety variable, glaucomatous progression, was analyzed by a McNemar test (Book 1978). Since this was a pilot trial the study was not powered for sample size. Age and intraocular pressure were analyzed by a t-test. Visual field, visual acuity, and optic disc were all analyzed by a Wilcoxon sign rank test. Gender, right/left eye, presence of cardiovascular disease, types of pre-study glaucoma surgical procedures, cardiovascular diagnosis, and intra-study glaucoma surgical procedures were analyzed by a McNemar test (Book 1978). Race and glaucoma medication history were evaluated by a chi square test.

Results
Patients

This analysis included 250 patients. From this, 50 matched pairs were compiled into the blood flow (dorzolamide, dorzolamide/timolol fixed combination) and non-blood flow (control) groups. The classification of medications used for this trial is presented in Table 1. Patient characteristics are shown in Table 2. There were no significant differences between groups for any parameter except the dorzolamide group had marginally greater baseline visual field damage (p = 0.05) and a greater number of laser trabeculoplasties prior to the study with dorzolamide (p = 0.01). All patients had primary open-angle glaucoma.

Glaucomatous progression

The matched patient pairs of patients in whom one progressed, including age, intraocular pressure and cardiovascular history, are shown in Table 3. The mean intraocular pressure in the dorzolamide group was 15.8 ± 2.4 and 15.8 ± 2.0 mmHg in the control group (p = 0.87). In the control group 7 patients progressed (14%) and 2 (4%) in the dorzolamide group during follow-up (p = 0.09). This was not a significant difference. The mean follow-up time for the progressed patients in the study for the control group was 26.4 ± 17.5 and 38.9 ± 14.9 months in the dorzolamide group (p = 0.43). For the stable patients the mean follow-up time for the progressed patients in the control group was 59.6 ± 2.2 and 58.4 ± 7.4 months in the dorzolamide group (p = 0.22).

Table 2 Patient characteristics

		Control (%)	Dorzolamide (%)	p value
Race				
	Caucasian	26 (52)	31 (62)	0.57
	Black	22 (44)	16 (32)	
	Asian	1 (2)	1 (2)	
	Hispanic	1 (2)	2 (4)	
Gender				
	Male	18 (36)	20 (40)	0.73
	Female	32 (64)	30 (60)	
Age				
	Mean	63.6 ± 8.6	63.8 ± 10.6	0.81
	≥40	0 (0)	1 (2)	
	41–50	5 (10)	7 (14)	
	51–60	12 (24)	10 (20)	
	61–70	22 (44)	17 (34)	
	71–80	11 (22)	13 (26)	
	80≤	0 (0)	2 (4)	
Eye				
	Right	23 (46)	25 (50)	0.84
	Left	27 (54)	25 (50)	
Visual acuity				
	20/20–20/25	29 (58)	22 (44)	0.50
	20/30–20/50	15 (30)	22 (44)	
	20/60–20/70	3 (6)	3 (6)	
	20/80–20/200	2 (4)	2 (4)	
	7/200–20/400	1 (2)	1 (2)	
Visual field defects				
0	Peripheral constriction or none	28 (56)	22 (44)	0.05
1	Seidel's scotoma/paracentral scotoma/nasal step	11 (22)	8 (16)	
2	Arcuate scotoma – one hemifield	8 (16)	14 (28)	
3	Arcuate scotoma – two hemifields	3 (6)	5 (10)	
4	Deep diffuse depression	0 (0)	1 (2)	
Fundus examinations findings				
0	Normal	2 (4)	1 (2)	0.07
1	Neural rim thinning	35 (70)	30 (30)	
2	Neural rim notching or saucerization	12 (24)	15 (30)	
3	Thin nasal rim	0 (0)	1 (2)	
4	Total glaucomatous cupping	1 (2)	3 (6)	
Pre-study enrollment glaucoma surgeries				
	Laser trabeculoplasty	14 (28)	28 (56)	0.01
	Trabeculectomy	2 (4)	0 (0)	0.20
Intra-study enrollment glaucoma surgeries				
	Laser trabeculoplasty	8 (16)	12 (24)	0.47
	Trabeculectomy	0 (0)	1 (2)	0.40
	Argon laser iridotomy	0 (0)	1 (2)	0.40
Cardiovascular history				
	Yes	19 (38)	19 (38)	1.00
	No	31 (62)	31 (62)	
Cardiovascular diagnosis (>1 incidence)				
	Hypertension	15 (30)	17 (34)	1.00
	Coronary artery disease	3 (6)	1 (2)	0.62
	Arrhythmia	1 (2)	1 (2)	0.48

Table 3 Matched pairs (^aProgressed)

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Pair #	Age (years)	Control Cardiac history	IOP (mmHg)	Dorzolamide Age (years)	Cardiac history	IOP (mmHg)
1	69	Yes	16	66	Yes	17
2	58	Yes	16	64	Yes	17
3	61	No	15	62	No	16
4	46	No	16	46	No	16
5	54	No	15	60	No	16
6	59	No	16	56	No	17
7	71	No	16	61	No	18
8	69	Yes	13	68	Yes	13a
9	65	Yes	18	75	Yes	19
10	78	No	17	80	No	19
11	53	No	16	48	No	18
12	53	No	13	63	No	13
13	62	No	17	60	No	18
14	77	Yes	16*	83	Yes	14
15	54	No	17	55	No	17
16	60	No	17	60	No	16
17	49	Yes	19	46	Yes	21
18	58	No	14	49	No	16
19	60	No	17	55	No	18
20	70	No	12	71	No	11
21	59	No	13	63	No	12
22	74	No	15	71	No	15
23	69	Yes	18	76	Yes	16
24	74	No	14	76	No	16
25	50	No	16	50	No	14
26	63	No	12	64	No	12
27	73	Yes	16	75	Yes	16
28	53	No	19	49	No	19
29	76	No	14	81	No	12
30	76	No	16	70	No	17
31	63	No	16	58	No	14
32	74	Yes	13	78	Yes	14
33	69	No	17	66	No	19
34	58	No	18	53	No	16
35	67	Yes	17a	68	Yes	17
36	64	No	19a	63	No	20
37	70	Yes	15a	79	Yes	14
38	68	No	20a	76	No	18
39	65	Yes	18	72	Yes	18
40	67	Yes	15a	64	Yes	13
41	71	Yes	16	72	Yes	15
42	44	No	13	46	No	11
43	65	No	12	71	No	13*
44	61	Yes	19a	55	Yes	17
45	67	Yes	15	68	Yes	16
46	76	Yes	17	70	Yes	17
47	66	No	15	57	No	14
48	61	No	14	69	No	15
49	63	Yes	14	62	Yes	12
50	49	Yes	19	40	Yes	18

Abbreviations: IOP, intraocular pressure.

These follow-up times differences were not statistically different for either progressed or stable patients.

The distribution of the intraocular pressure for the matched pairs, and whether or not they progressed, are shown in Figure 1. The two patients who progressed in the dorzolamide group had lower intraocular pressures (both 13 mmHg) than in the control group (range 15–20 mmHg).

Discussion

Dorzolamide is a topical anhydrase inhibitor that is an active ingredient in two commercially available formulations (Trusopt™ and Cosopt™, Merck & Co., Whitehouse Station, NJ, USA). Dorzolamide is chemically related to acetazolamide (Diamox™, Wyeth, Madison, NJ, USA), a systemic carbonic anhydrase inhibitor. However, acetazolamide also has a systemic effect on the central nervous system vasodilation (Bonte et al 1988). The molecular basis for this action is not yet understood. Dorzolamide has also been shown to have a vascular effect in the eye. Consistent with this finding, Harris and associates have shown in several studies using color doppler imaging that dorzolamide as well as the dorzolamide/timolol fixed combination in normals, primary open-angle, and low tension glaucoma patients may increase red blood cell velocity in retinal vessels (Harris et al 2000, 2001, 2003a).

Theoretically this positive ocular blood flow effect could help limit progression to glaucoma (Bernd et al 2001). Poor blood flow has been associated with the progression of glaucoma by several lines of evidence (Cioffi 2001). First, epidemiologic factors: a clinical history of generally systemic atherosclerotic or vasospastic disease has been linked to a greater incidence of elevated intraocular pressure and primary open-angle glaucoma (Stewart 1990). Specific related symptoms and signs have been: elevated blood pressure, cardiovascular disease, peripheral vasospasm, migraines, diabetes, decreased diastolic ocular perfusion pressure, and night-time blood pressure dips, as well as symptoms of cold hands and feet (Shields 1982; Gasser et al 1990; Stewart 1990; Akarsu and Bilgili 2004; Fraser and Wormald 2004; Zimmerman et al 2004). Second, clinical ocular hemodynamics in glaucoma and ocular hypotensive patients have
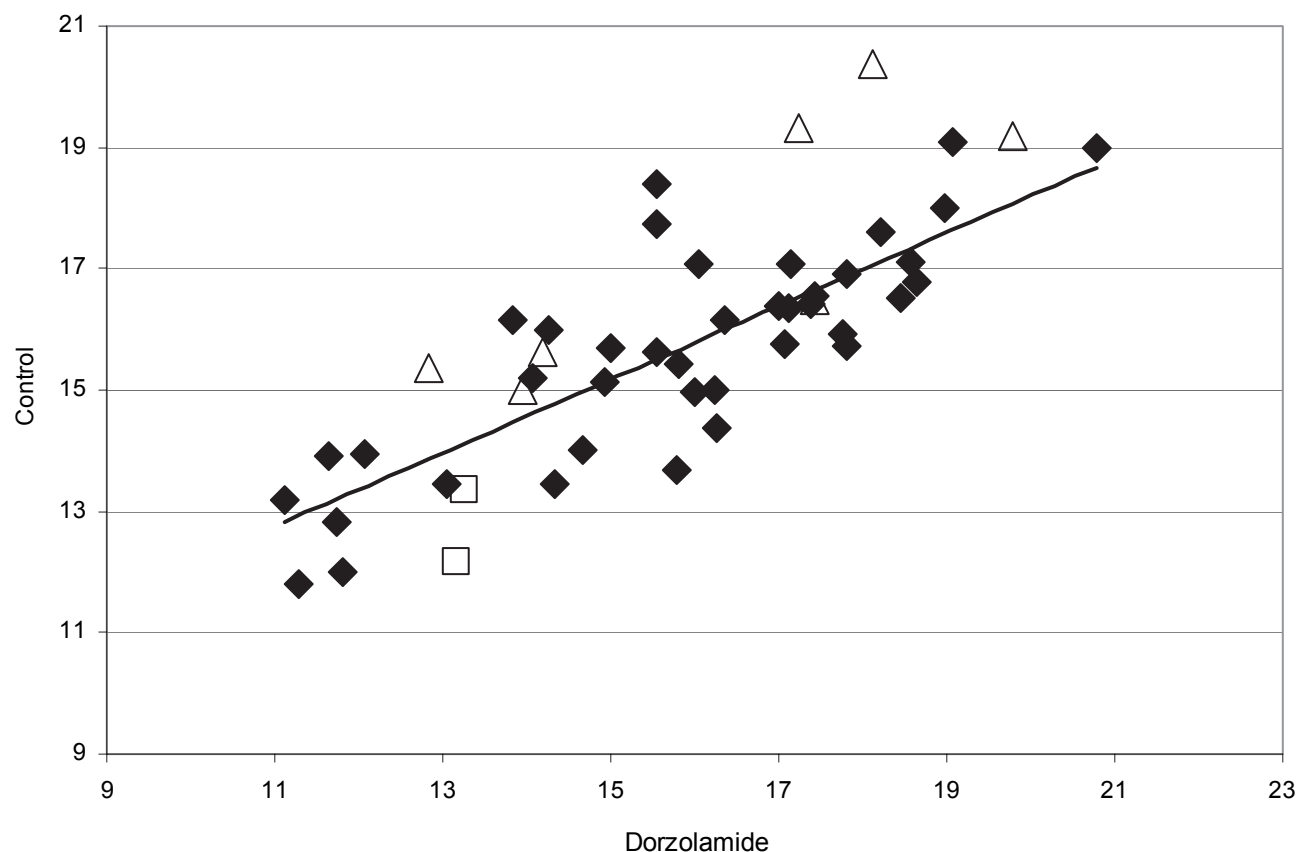

Figure 1 The figure shows the distribution and linear regression of the intraocular pressure for the matched pairs and whether they progressed for each matched pair on dorzolamide (square), control patients (triangle), and matched pairs that did not progress (diamond).

shown worsened ocular blood flow measures, compared with normals, including: peak blood flow (probably choroidal), retinal blood flow, resistivity index and red blood cell velocity (Stewart 1998; Akarsu and Bilgili 2004; Galassi et al 2003). In addition, several other studies have specifically noted that progressed glaucoma patients demonstrate worse blood flow indices compared to non-progressed patients (Galassi et al 2003; Satilmis et al 2003; Flammer et al 2002; Gherghei et al 2000). Third, systemic vascular disease relationships: Stroman and co-workers have shown that patients with low tension glaucoma have increased white matter lesions in the brain indicative of central nervous system vascular disease (Gherghei et al 2000). In addition, Harris and associates noted blood flow abnormalities in the central carotid artery in patients with glaucoma indicating a potential association to atherosclerotic disease in the central nervous system vasculature (Harris et al 2003b).

The above studies are limited by several factors: first, the epidemiologic association of cardiovascular history to glaucoma is not completely consistent; second, epidemiologic, as well as clinical systemic blood flow, relationships to glaucoma have not been shown to be causal, but may be only a casual association; and third, it remains unclear whether reduced clinical blood flow measurements in glaucoma are a primary (pathogenic) or a secondary effect (due to a reduced blood flow requirement from glaucomatous optic nerve tissue loss). Unfortunately, studies have not yet evaluated baseline blood flow parameters to long-term clinical outcomes or shown that improving these blood flow parameters prevents progression.

The purpose of this pilot study was to evaluate the long-term progression rates of primary open-angle glaucoma patients treated with an assumed blood flow active ocular hypotensive agent (ie, dorzolamide group) versus a non-blood flow active agent (control group). Patients were matched 1:1 by intraocular pressure so any differences in progression rates between groups might be related to non-pressure related factors.

This study showed over 5 years that patients in the dorzolamide group progressed in 4% of cases compared with 14% in the control group. In addition, progression was delayed in the dorzolamide-treated patients (39 months) compared with the control group patients (26 months). Since patients were matched for intraocular pressure, any divergence in progression rates between treatment groups should not have resulted from differences in the ocular hypotensive treatment effect. The differences found between the groups in the study, however, were not statistically significant and represent only a trend towards an improvement in progression in the dorzolamide group. Although progression rates were difficult to compare between studies, in our study the percentage of patients who worsened were comparable to CIGTS and less than the EMGT (Lichter et al 2001; Heijl et al 2002). However, progression rates could have varied with a larger patient sample in our study.

Few differences existed between groups besides slightly greater visual field damage and a greater number of laser trabeculoplasties prior to the study with dorzolamide. Some authors have speculated that patients with greater visual field damage are more likely to progress at lower pressures, which could have led towards greater progression for the dorzolamide group (Stewart et al 1993). However, a greater number of trabeculoplasties should not have influenced the results because the pressures were matched between treatment groups.

An additional finding was that the progressed patients in the dorzolamide group had lower mean pressures (both 13 mmHg) over the follow-up period compared with the control group (range 15–20 mmHg). The reason for this was not apparent. It may suggest that patients who progressed in the dorzolamide group potentially had particularly diseased eyes, or poor perfusion pressure, and progressed despite the low pressure and any potential blood flow effect from dorzolamide. Previous studies have noted that progression of glaucoma happens at a very low rate at pressures of 12–13 mmHg (Mao et al 1991; Stewart et al 1993; AGIS Investigators 2000; Stewart et al 2000).

Although this study raises the question of whether a potential ocular blood flow effect might influence long-term clinical outcomes in glaucoma, the results are based on several unproven assumptions: first, the observed clinical trend of reduced progression in the dorzolamide group was real and was not a result of mere chance; second, dorzolamide had an actual positive clinical blood flow effect; third, the medicines in the control group had no positive clinical blood flow or neuroprotective effect; and last, the matching criteria were adequate to eliminate other clinical factors that could have accounted for the difference in the progression rate between treatment groups.

Although the results were not statistically significant, this pilot trial demonstrated a trend towards less glaucomatous progression in patients treated with an assumed active blood flow product. In addition, progression was delayed and occurred at lower pressures in the active blood flow group. Consequently, the clinical relevance of this pilot trial is to suggest that future prospective, long-term, clinical outcome

studies in patients treated with a medicine with a positive ocular blood flow effect may be warranted.

This study did not evaluate dorzolamide or other active blood flow agents in a prospective, controlled, masked fashion. Although this study had matching criteria of intraocular pressure, cardiac history, and age, other potentially important criteria such as stage of the disease were not matched. In addition, medicines with a neuroprotective or blood flow effect were allowed in the control group and in the active treatment group apart from dorzolamide in order to gain qualified patients, even though these medicines could have potentially affected progression rates in both groups. In addition, investigators were not masked to treatments when collecting data for this study. Long-term studies are needed to confirm any pathogenesis of reduced blood flow related to glaucoma and the benefit of treatment.

Acknowledgments

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