

Tolerability and effectiveness of preservative-free dorzolamide–timolol (preservative-free COSOPT®) in patients with open-angle glaucoma or ocular hypertension

Cindy Hutnik¹
David Neima²
Fahim Ibrahim³
Robert Scott⁴
Julie Vaillancourt⁵
Denis Haïne⁵
John S Sampalis⁵
Natacha Bastien⁶
Sylvain Foucart⁶

¹Ivey Eye Institute, St Joseph Healthcare, London, Ontario, Canada; ²New Westminster, British Columbia, Canada; ³Point Edward, Ontario, Canada; ⁴Kentville, Nova Scotia, Canada; ⁵JSS Medical Research, Westmount, Quebec, Canada; ⁶Merck Frosst Canada Ltd, Kirkland, Quebec, Canada

Purpose: To assess the effect of preservative-free dorzolamide–timolol on nonvisual symptoms and intraocular pressure (IOP) in newly diagnosed and untreated patients with open-angle glaucoma or ocular hypertension.

Methods: This was a prospective, 8-week, open-label, Canadian multicenter study. All patients were treated with preservative-free dorzolamide–timolol formulation. The primary outcome was the change in the nonvisual symptom score of the Glaucoma Symptom Scale (GSS-SYMP-6) from baseline to 8 weeks. Secondary effectiveness outcome measures were absolute and percent changes in IOP from baseline to 4 and 8 weeks.

Results: One hundred and seventy-eight patients were enrolled. Mean (SD) age was 65.6 (12.1) years and 90 (50.6%) were females. There were 92 patients diagnosed with open-angle glaucoma, 62 with ocular hypertension, and 23 with both diseases (diagnosis was missing for one patient). The mean (SD) GSS-SYMP-6 score increased from 73.6 (21.8) at baseline to 76.1 (20.7) at 8 weeks ($P = 0.097$). Mean (SD) IOP significantly decreased by 11.7 (5.1) mmHg at 4 weeks ($P < 0.001$) and by 11.5 (5.3) mmHg at 8 weeks ($P < 0.001$), representing reductions of -38.5% ($P < 0.001$) and -38.0% ($P < 0.001$), respectively.

Conclusion: Preservative-free dorzolamide–timolol does not increase eye discomfort while significantly reducing IOP in patients with open-angle glaucoma or ocular-hypertension.

Keywords: open-angle glaucoma, ocular hypertension, GSS-SYMP-6, intraocular pressure, dorzolamide–timolol, preservative-free

Introduction

Open-angle glaucoma is a chronic progressive disease characterized by asymptomatic elevation of intraocular pressure (IOP), progressive optic nerve damage, and visual field loss that can lead to blindness.¹ Glaucoma is the second leading cause of blindness worldwide² and in Canada,³ and its incidence increases with advancing age.^{4,5}

Currently, the goal of glaucoma therapy is to reduce the rate of retinal ganglion cell loss by decreasing IOP.⁶ Since open angle-glaucoma and ocular hypertension are progressive chronic conditions, their management requires long-term and even life-long treatment. As with all chronic conditions, treatment benefits must be balanced against possible risk for side effects. In addition, tolerability of long-term treatment becomes an important factor contributing to therapeutic effectiveness given its impact on compliance. Therefore, the aim of glaucoma therapy is the reduction of IOP and

Correspondence: Cindy Hutnik
Department of Ophthalmology and Pathology, Ivey Eye Institute, St Joseph Health Care London, 268 Grosvenor Street, London, Ontario, N6A 4V2
Tel +1 519 646 6272
Fax +1 519 646 6410
Email cindy.hutnik@sjhc.london.on.ca

preservation of visual field and vision while reducing the impact of chronic therapy and potential side effects on the patients' quality of life.

Dorzolamide, a topical carbonic anhydrase inhibitor, and timolol, a nonselective beta receptor blocking agent, are both effective in the management of elevated IOP, and are well established as ocular hypotensive treatments. Further, they have an additive IOP-lowering effect when administered concomitantly.⁷ Several clinical trials have demonstrated the efficacy of dorzolamide–timolol fixed combination in the treatment of open-angle glaucoma and ocular hypertension.^{8–19} However, the preservative agents included in the formulation of these eye-drop therapies have been shown to decrease the stability of the precorneal tear film and to have a detergent effect on the lipid layer; resulting in increased evaporation, dry-eyes,²⁰ and irritation.²¹ Preservative-free eye drops may therefore be useful in the efforts to protect and maintain ocular surface integrity, especially as over 50% of patients treated for glaucoma have concurrent ocular surface disorders.^{20,22,23} Indeed, preservative-free medications could provide an effective alternative for long-term treatment of glaucoma and ocular hypertension for patients who are sensitive to a preservative and those with a history of dry or irritated eyes.

The principal aim of this study was to describe the change in nonvisual ocular symptoms in newly diagnosed patients with open-angle glaucoma or ocular hypertension treated with a preservative-free dorzolamide-timolol formulation.

Materials and methods

Study design

This was an 8-week prospective, multicenter, open-label study performed in 18 Canadian ophthalmologists' clinics between May 2007 and October 2008. Assessments were performed at baseline (week 0), and at 4 and 8 weeks of treatment at the treating ophthalmologists' clinics. At each study visit, patients completed the six-item nonvisual symptom scale (GSS-SYMP-6) extracted from the 10-item glaucoma symptom scale (GSS).²⁴ The six nonvisual symptoms assessed were: i. burning, smarting and stinging, ii. tearing, iii. dryness, iv. itching, v. soreness and tiredness, and vi. feeling of something in the eye. Patients were asked to rate each of these six nonvisual symptoms using a five-point Likert Scale with 0 being very bothersome and 4 representing the absence of the symptom. The score of this scale was transformed between 0 and 100 with lower scores indicating higher severity of the nonvisual symptoms. A score of 100 was the best possible score and positive changes indicate improvement in

the patient's condition. In addition, at each study visit, the treating ophthalmologists measured the IOP in patients' both eyes using a calibrated Goldmann's applanation tonometer. This was calculated as the mean of two consecutive and independent measures in the same eye. Patients were assessed at any time during the day. However, each patient was assessed at approximately the same time of the day at all visits.

The study was approved by an Independent Ethics Review Board (Institutional Review Board Services, Aurora, Ontario) and was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Good Clinical Practice guidelines", the World Medical Association Declaration of Helsinki and all applicable local regulations. A written informed consent was obtained from every patient prior to conducting any study related procedures including the evaluation of study eligibility and enrolment.

Patients

Eligible patients (≥ 18 years) were recently diagnosed with open-angle glaucoma or ocular hypertension according to the Canadian Ophthalmological Society evidence-based clinical practice guidelines.²⁵ Open-angle glaucoma was diagnosed when there was evidence of glaucomatous optic neuropathy (GON), with or without elevated IOP, while ocular hypertension was diagnosed when IOP was elevated, but without evidence of GON or visual field damage. Eligible patients also had an IOP of ≥ 27 mmHg in at least one eye and a baseline GSS-SYMP-6 total score of 75 or less. All were treatment-naive. In addition, patients may have been either sensitive to a preservative or had "less than perfect" ocular surface issues, as per the clinical judgment of the treating ophthalmologist.

Patients were excluded from the study if they had any fundus pathology likely to change during the study or to influence IOP, hypersensitivity to any component of preservative-free dorzolamide–timolol, severe renal impairment (serum creatinine >150 $\mu\text{mol/L}$ or creatinine clearance <30 mL/min), or any contraindication to the use of preservative-free dorzolamide–timolol including bronchospasm (eg, bronchial asthma or any history of bronchial asthma and chronic obstructive pulmonary disease) or sinus bradycardia, or second or third degree AV block, or overt cardiac failure or cardiogenic shock). Patients with a history of diabetic retinopathy were eligible for inclusion in the study. Prohibited concomitant medications were carbonic anhydrase inhibitors (systemic and topical), systemic or dermatological medications known to affect the IOP

(eg, clonidine, corticosteroids or oral beta-blocking agents), and any medications containing one of the following preservative agents: benzalkonium chloride, benzododecinium bromide, or stabilized oxychloro complex.

Treatment

All patients were treated with the preservative-free formulation of dorzolamide–timolol (COSOPT® without benzalkonium chloride as preservative, Merck Frosst Canada Ltd, Kirkland, Canada) for eight weeks on a self-administered regimen of one drop, twice daily in the morning and bedtime, in each affected eye.

Outcome measures

The primary outcome measure was the change in GSS-SYMP-6 score from baseline to 8 weeks of treatment. Secondary outcome measures were the mean absolute change in GSS-SYMP-6 score from baseline to 4 weeks of treatment. The presence and severity of the nonvisual symptoms in patients' worse eye, defined as the eye with the highest IOP measure at baseline, were also described at each visit. Therapeutic effectiveness outcomes were the absolute and percent changes in IOP measured in the worse eye from baseline to 4 and 8 weeks of treatment. Patient and ophthalmologist satisfaction with treatment after 8 weeks were assessed with a five-point Likert scale question ranging from 0 (very dissatisfied) to 4 (very satisfied). Compliance with study treatment was also assessed by self-reporting at 4 and 8 weeks during clinic visits. Patients who reported missing more than 20% of scheduled doses were considered non-compliant. Safety was assessed by the incidence of adverse events that occurred during treatment and up to 14 days after study drug discontinuation.

Statistical methods

A difference of seven points was observed in the SYMP-6 validation study,²⁴ in which patients with glaucoma had a mean (SD) score of 78 (23) compared to 85 (21) for the reference group. The present study sought to detect this clinically significant difference of seven points. With an 80% power and allowing for 10% drop out rate, a minimum of 170 patients were to be enrolled.

Descriptive statistics including the mean and standard deviation for continuous variables and frequency distributions for discrete variables were reported. The statistical significance of the change in GSS-SYMP-6 score from baseline to 4 and 8 weeks was assessed with the Student's *t*-test for paired observations. The 95% confidence intervals of the mean

change were also computed as measures of precision and to allow inference to the target population. χ^2 statistics were used to test the difference in the presence of nonvisual symptoms and to assess the change in the distribution of the symptom severity from baseline to 4 and 8 weeks of treatment.

The statistical significance of the mean absolute and percent change in IOP was assessed with the Student's *t*-test for paired observations. For this outcome, 95% confidence intervals were also computed. The observed mean absolute change in IOP from baseline to 4 and 8 weeks was compared to the conventional value of zero (Ho: $\delta = 0$ mmHg) and to the *a priori* established value of -4.0 mmHg (Ho: $\delta \leq -4.0$ mmHg). The test value for the comparison of the observed mean percent change in IOP was of -20% (Ho: $\delta \leq -20.0\%$). An absolute change of -4.0 mmHg or percent change of -20.0% were considered as the minimum for clinical significance.

All analyses were based on observed cases and no imputation methods were used for replacing missing data. As per the intention-to-treat (ITT) principle, all patients with outcome measurements at baseline and one of the follow-up visits were included in the analyses regardless of protocol violations and compliance with treatment. The minimum level of statistical significance was *a priori* defined at 5%. All statistical analyses were performed using STATA (version 10.0; College Station, TX) and SPSS (version 12.0 for Windows; SPSS Inc, Chicago, IL).

Results

Patient disposition

A total of 178 patients formed the ITT population and were included in the study. Of these, 169 (94.9%) and 176 (98.9%) were assessed at 4 and 8 weeks, respectively. There were 9 (5.1%) patients who were discontinued from the study: 2 (1.1%) patients withdrew consent, 3 (1.7%) were lost to follow-up, 1 (0.6%) experienced a serious adverse event, and 3 (1.7%) were discontinued for other reasons. Seven of the discontinued patients were retrieved drop-outs that were included in the 8-week assessment based on their visit date.

Patient demographics

The patient demographics are summarized in Table 1. The mean (SD) age of the 178 patients included in the study was 65.6 (12.1) years; 21 (11.8%) were ≤ 52 years of age and 58 (32.6%) were > 72 years. The majority were Caucasian ($n = 168$; 94.4%) and 90 (50.6%) were females. A total of 92 patients were diagnosed (worse eye) with open-angle glaucoma, 62 with ocular hypertension, and 23 with both

Table 1 Demographics of the 178 patients included in the study

Characteristics	n	%
Age (years) ^a		
≤52	21	11.8
>52 to ≤72	97	54.5
>72	58	32.6
Gender		
Male	88	49.4
Female	90	50.6
Race		
Caucasian	168	94.4
Black	3	1.7
Hispanic	2	1.1
Asian	4	2.3
Other	1	0.6
Worse eye ^b		
Left eye	97	54.5
Right eye	81	45.5
Presence of open-angle glaucoma		
Left eye	91	51.1
Right eye	102	57.3
Presence of ocular hypertension		
Left eye	76	42.7
Right eye	82	46.1
Presence of glaucoma or ocular hypertension in both eyes	125	70.2
Medical history		
Family history of open-angle glaucoma or ocular hypertension	42	23.6
Type I diabetes	4	2.3
Type II diabetes	37	20.8
Hypertension	53	29.8
Myopia	35	19.7
Migraine/headache	18	10.1

Notes: ^aThe age of 2 (1.1%) patients was unknown. ^bThe worse eye was defined as the eye with the highest intraocular pressure measure at baseline.

diseases; diagnosis was missing for 1 patient. There were 125 patients (70.2%) who had both eyes affected by either open-angle glaucoma or ocular hypertension.

Effectiveness

The GSS-SYMP-6 scores for the worse eye were available for 122 patients at baseline, 115 at 4 weeks, and 113 at

8 weeks. The mean (SD) GSS-SYMP-6 score increased from 73.6 (21.8) at baseline to 74.5 (19.3) at 4 weeks and 76.1 (20.7) at 8 weeks of treatment (Table 2). The mean (SD) absolute changes in GSS-SYMP-6 scores from baseline to 4 and 8 weeks of treatment were 1.8 (16.9) and 3.2 (20.2), respectively (Table 2).

Table 3 describes the presence and severity of nonvisual symptoms in the worse eye at baseline, 4, and 8 weeks of treatment. While the presence of burning, smarting, and stinging symptoms significantly increased from 28.0% at baseline to 63.0% at 4 weeks ($P < 0.001$), and 61.9% at 8 weeks ($P < 0.001$), there was no statistical difference in the presence of these symptoms between 4 and 8 weeks of treatment ($P = 0.859$). The proportion of patients with itching was reduced from 49.2% at baseline to 35.7% at 4 weeks ($P = 0.028$) and 35.2% at 8 weeks ($P = 0.023$). From baseline to 8 weeks of treatment, decreases in the presence of the following symptoms were observed: dryness (39.4% to 28.8%; $P = 0.074$), and soreness and tiredness (49.2% to 36.0%; $P = 0.032$). The severity profile of these symptoms did not change during the course of the study.

The IOP measurements at each study visit and the mean absolute changes in IOP from baseline to 4 and 8 weeks of treatment are presented in Table 4. The mean (SD) IOP decreased from 29.6 (4.2) mmHg at baseline to 18.1 (3.7) mmHg at 4 weeks and 18.1 (3.9) mmHg at 8 weeks of treatment. The mean (SD) absolute reduction in IOP from baseline to 4 weeks was -11.7 (5.1) mmHg ($P < 0.001$) and -11.5 (5.3) mmHg ($P < 0.001$) at 8 weeks. These changes were significantly higher than the test value of -4.0 mmHg ($P < 0.001$). At 4 and 8 weeks, a total of 156 (92.3%) and 158 (89.8%) patients achieved a clinically significant reduction in IOP of at least 4.0 mmHg, respectively.

Figures 1 and 2 depict the distribution of the mean percent change in IOP from baseline to 4 and 8 weeks of treatment. The mean (SD) percent reduction in IOP was 38.5% (13.0) at 4 weeks ($P < 0.001$) and 38.0% (14.73) at

Table 2 Glaucoma nonvisual symptoms scale (GSS-SYMP-6) measurements

Visits	N	Mean (SD)	95% CI		P-values
			Lower limit	Upper limit	
Baseline (week 0)	122 ^a	73.6 (21.8)	69.5	77.1	–
Week 4	115 ^b	74.5 (19.3)	71.1	78.1	–
Absolute change from baseline	114 ^c	1.8 (16.9)	–1.3	4.9	0.260
Week 8	113 ^d	76.1 (20.7)	72.3	79.7	–
Absolute change from baseline	111 ^e	3.2 (20.2)	–0.6	7.0	0.097

Notes: ^aThe GSS-SYMP-6 was not completed for both eyes at baseline by 56 of the 178 patients. ^bThe GSS-SYMP-6 was not completed for both eyes at week 4 by 54 of the 169 patients. ^cThe GSS-SYMP-6 was not completed for both eyes at baseline and week 4 by 55 of the 169 patients. ^dThe GSS-SYMP-6 was not completed for both eyes at week 8 by 63 of the 176 patients. ^eThe GSS-SYMP-6 was not completed for both eyes at baseline and week 8 by 65 of the 176 patients.

Abbreviation: CI, confidence interval.

Table 3 Presence and severity of the nonvisual symptoms in the worse eye

Nonvisual symptoms (GSS-SYMP-6)*	Baseline (N = 132) ^a		Week 4 (N = 127) ^{b,c}		Week 4 vs Baseline P-value	Week 8 (N = 125) ^{d,e}		Week 8 vs Baseline P-value
	n	%	n	%		n	%	
Burning, smarting, stinging								
Absence of symptom	95	72.0	47	37.0	<0.001	48	38.1	<0.001
Presence of symptom	37	28.0	80	63.0		78	61.9	
Very bothersome	5	13.5	6	7.5	0.356	6	7.7	0.219
Somewhat bothersome	11	29.7	21	26.3		18	23.1	
A little bothersome	19	51.4	50	62.5		50	64.1	
Not at all bothersome	2	5.4	3	3.8		4	5.1	
Tearing								
Absence of the symptom	75	56.8	61	48.0	0.158	64	51.2	0.367
Presence of the symptom	57	43.2	66	52.0		61	48.8	
Very bothersome	7	12.3	4	6.1	0.129	7	11.5	0.233
Somewhat bothersome	18	31.6	18	27.3		14	23.0	
A little bothersome	29	50.9	37	56.1		33	54.1	
Not at all bothersome	3	5.3	7	10.6		7	11.5	
Dryness								
Absence of the symptom	80	60.6	87	68.5	0.185	89	71.2	0.074
Presence of the symptom	52	39.4	40	31.5		36	28.8	
Very bothersome	13	25.0	6	15.0	0.106	4	11.1	0.057
Somewhat bothersome	19	36.5	11	27.5		9	25.0	
A little bothersome	15	28.8	19	47.5		22	61.1	
Not at all bothersome	5	9.6	4	10.0		1	2.8	
Itching								
Absence of the symptom	67	50.8	81	64.3	0.028	81	64.8	0.023
Presence of the symptom	65	49.2	45	35.7		44	35.2	
Very bothersome	5	7.7	1	2.2	0.220	3	6.8	0.274
Somewhat bothersome	15	23.1	8	17.8		5	11.4	
A little bothersome	40	61.5	32	71.1		33	75.0	
Not at all bothersome	5	7.7	4	8.9		3	6.8	
Soreness, tiredness								
Absence of the symptom	67	50.8	81	63.8	0.035	80	64.0	0.032
Presence of the symptom	65	49.2	46	36.2		45	36.0	
Very bothersome	6	9.2	1	2.2	0.217	2	4.4	0.091
Somewhat bothersome	24	36.9	16	34.8		11	24.4	
A little bothersome	30	46.2	24	52.2		28	62.2	
Not at all bothersome	5	7.7	5	10.9		4	8.9	
Feeling of something in the eye								
Absence of the symptom	84	63.6	89	70.1	0.272	83	66.4	0.643
Presence of the symptom	48	36.4	38	29.9		42	33.6	
Very bothersome	6	12.5	4	10.5	0.472	6	14.3	0.544
Somewhat bothersome	11	22.9	8	21.1		7	16.7	
A little bothersome	29	60.4	22	57.9		25	59.5	
Not at all bothersome	2	4.2	4	10.5		4	9.5	

Notes: *Glaucoma symptom scale. ^aAt baseline, the GSS-SYMP-6 was not completed for the worse eye by 46 of the 178 patients. ^bAt week 4, the GSS-SYMP-6 was not completed for the worse eye by 42 of the 169 patients. ^cN = 126 for itching nonvisual symptom; at week 4, the itching nonvisual symptom was not completed for the worse eye by 43 of the 169 patients. ^dAt week 8, the GSS-SYMP-6 was not completed for the worse eye by 51 of the 176 patients. ^eN = 126 for burning, smarting and stinging symptoms; at week 8, burning, smarting and stinging symptoms were not completed for the worse eye by 50 of the 176 patients.

8 weeks ($P < 0.001$). A clinically significant IOP reduction of at least 20% at 4 and 8 weeks of treatment was observed for 153 (90.5%) and 154 (87.5%) patients, respectively.

Figure 3 summarizes the results of the patient and ophthalmologist global satisfaction with treatment rating after 8 weeks of therapy. After 8 weeks of treatment, 144 (81.8%) patients were either satisfied or very satisfied with

the preservative-free dorzolamide-timolol formulation, while 9 (5.1%) patients were either dissatisfied or very dissatisfied with treatment. After 8 weeks of treatment, the ophthalmologists were either satisfied or very satisfied with the preservative-free dorzolamide-timolol formulation for 155 (88.1%) of the patients, while they were either dissatisfied or very dissatisfied for 7 (3.9%) of them.

Table 4 Intraocular pressure (IOP) measurements (mmHg) in the worse eye

Visits	N	Mean (SD)	95% CI		P-values	
			Lower limit	Upper limit	H ₀ : δ = 0	H ₀ : δ = -4
Baseline (Week 0)	178	29.6 (4.2)	29.0	30.2	–	–
Week 4	165 ^a	18.1 (3.7)	17.5	18.7	–	–
Absolute change from baseline	165 ^b	-11.7 (5.1)	-12.5	-10.9	<0.001	<0.001
Week 8	167 ^c	18.1 (3.9)	17.5	18.8	–	–
Absolute change from baseline	166 ^d	-11.5 (5.3)	-12.3	-10.7	<0.001	<0.001

Notes: ^aIOP measurement at week 4 was not available for 4 of the 169 patients. ^bIOP measurements at baseline and week 4 were not available for 4 of the 169 patients. ^cIOP measurement at week 8 was not available for 9 of the 176 patients. ^dIOP measurements at baseline and week 8 were not available for 10 of the 176 patients.
Abbreviations: SD, standard deviation; CI, confidence interval; δ, difference.

Adherence to treatment was high. There were 162 (95.8%) and 159 (90.3%) patients who were ≥80% compliant with treatment at 4 and 8 weeks, respectively. At 4 weeks, 107 (63.3%) patients reported perfect adherence (taking 100% of their medication) while another 55 (32.5%) reported adherence (taking 80%–99.9% of their study medication). Similar results were obtained at week 8, with 106 (60.2%) patients reporting perfect adherence and another 53 (30.1%) reporting adherence. The median missed dose at each visit was 0.0 drops.

Safety

During the course of this 8-week study, three serious adverse events were experienced by three patients. A 67-year-old

female experienced a retinal vein occlusion that was considered by the treating ophthalmologist to be probably not related to study medication. A 95-year-old male had nausea and another 61-year-old male experienced bradycardia. These two events were considered to be definitely related to the study medication; however, both patients recovered without any sequelae or permanent disability. The patient who had nausea discontinued study medication after 2 weeks of treatment.

Discussion

This was the first Canadian observational study aimed at assessing nonvisual ocular symptoms and the effectiveness

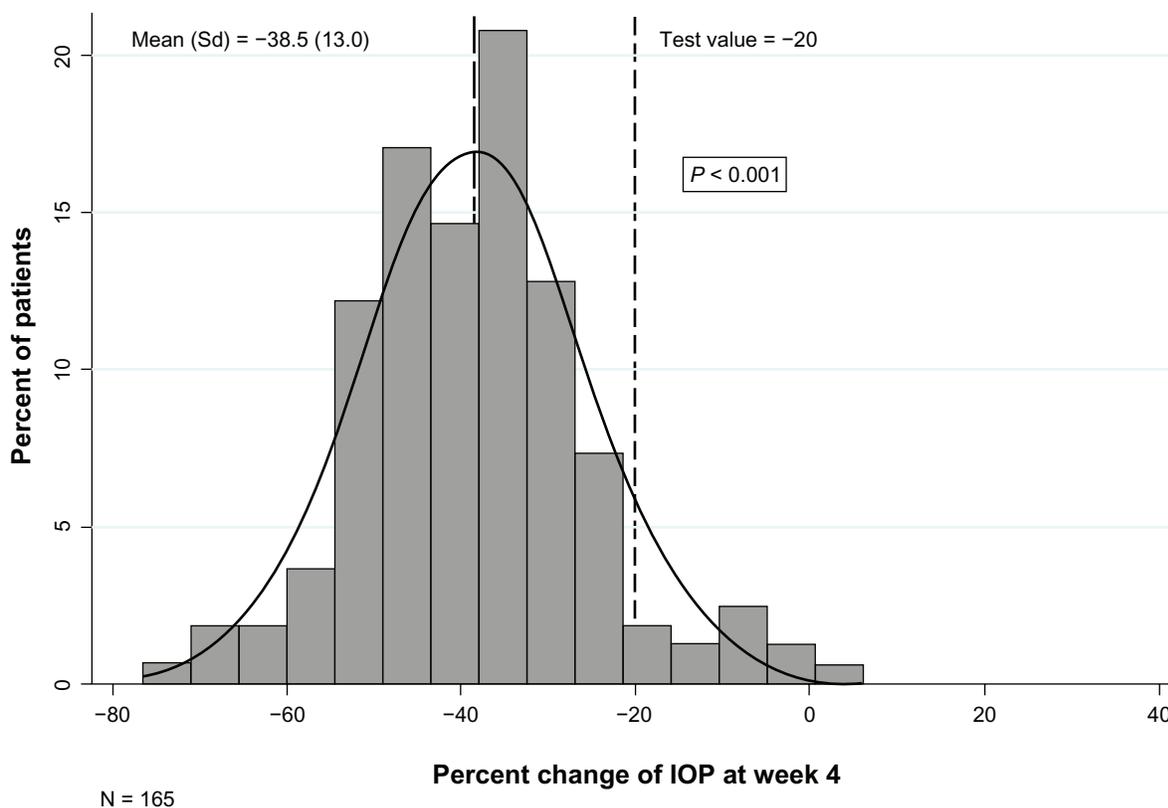


Figure 1 Percent change in intraocular pressure (IOP) of the worse eye between week 4 and baseline.

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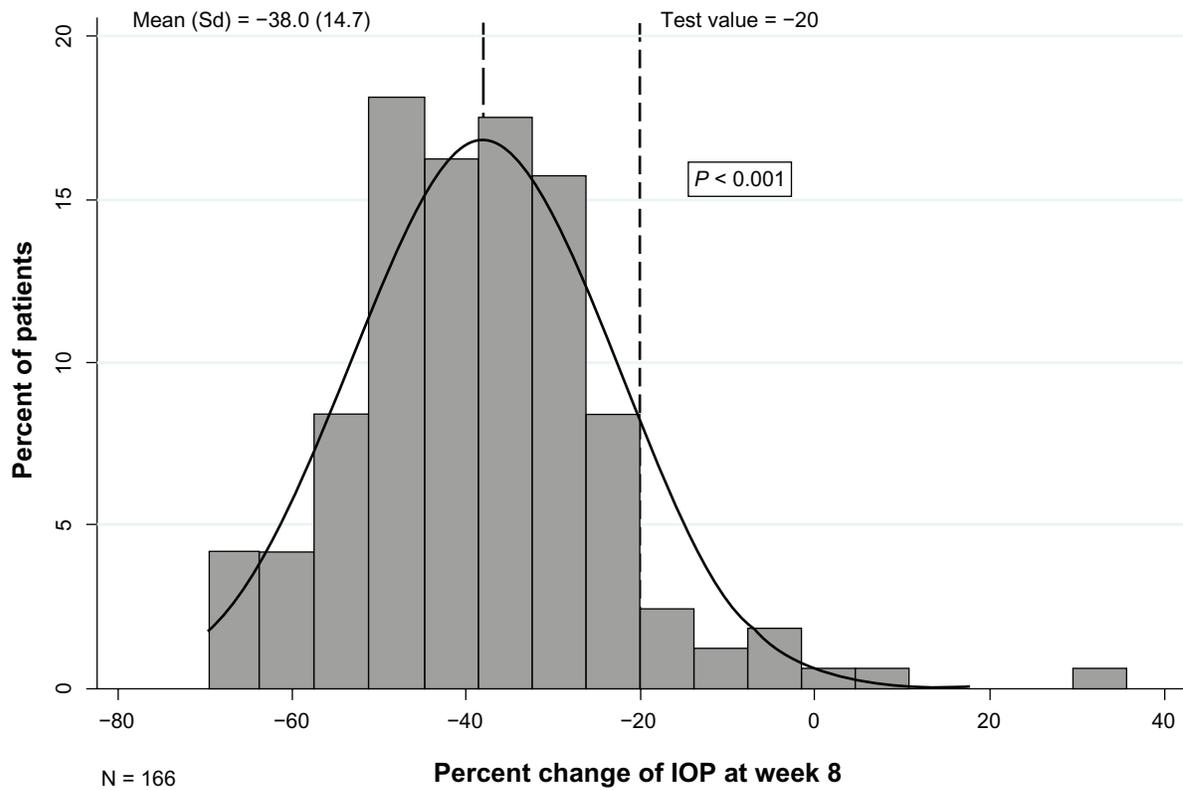


Figure 2 Percent change in intraocular pressure (IOP) of the worse eye between week 8 and baseline.

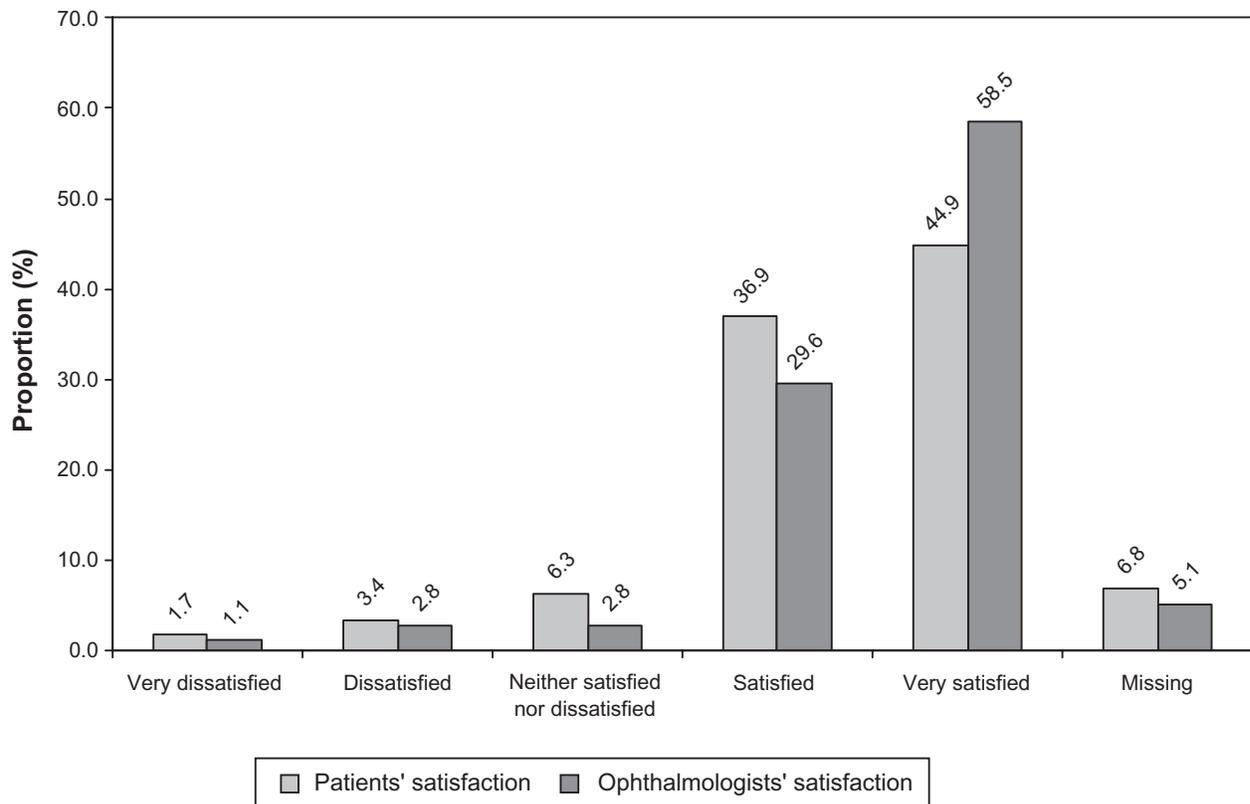


Figure 3 Patients' and ophthalmologists' global satisfaction with 8 weeks preservative-free dorzolamide-timolol treatment.

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of preservative-free dorzolamide–timolol formulation in a real-life setting. The results of this study showed that treatment with preservative-free dorzolamide–timolol does not increase discomfort related to nonvisual ocular symptoms, while maintaining therapeutic effectiveness in reducing IOP.

It is postulated that discomfort with eye-drop therapy can lead to patient discontinuation of treatment.^{26–28} While a small increase in GSS-SYMP-6 score (indicating improvement) was observed in the current study, this increase was neither statistically nor clinically significant. The use of the preservative-free formulation therefore did not increase eye discomfort, which may have been an important factor contributing to high compliance with therapy. This could result in optimization of long-term treatment effectiveness.

In this study, over 80% of patients and ophthalmologists were satisfied with the preservative-free dorzolamide–timolol formulation. From the perspective of the patient, the high level of satisfaction can be mainly explained by the reduction in dryness, itching, soreness, and tiredness in the eyes. This could contribute to improved quality of life during the course of treatment. From the perspective of the physician, the high level of satisfaction reported by the ophthalmologists may be due to the observed therapeutic effectiveness of the preservative-free dorzolamide–timolol formulation in reducing IOP. The magnitude of IOP reduction observed in these patients is likely associated with their treatment-naïve drug status since more robust IOP reduction is known to occur in treatment-naïve patients.

In the current study, self-administration of preservative-free dorzolamide–timolol during eight weeks produced an IOP reduction of approximately 40%, which exceeds the treatment targets established by the American Academy of Ophthalmology and the European Glaucoma Society. In fact, the American Academy of Ophthalmology currently recommends IOP lowering of at least 20% from baseline IOP²⁹ and the European Glaucoma Society recommends lowering of at least 30% from baseline IOP.³⁰

The observed change in IOP is comparable but higher than that generally reported by randomized clinical trials of dorzolamide–timolol,^{7,8,15,18,31–34} further supporting the efficacy of dorzolamide–timolol. Importantly, the present study indicates that the absence of preservative did not seem to thwart the efficacy. It is conceivable that by disrupting the corneal epithelium, preservatives partially contribute to ocular penetration and hence, therapeutic effectiveness. The results in this study suggest that preservative-induced effects on the ocular surface are not necessary for the drug

efficacy. Since there is no difference in efficacy between preserved and preservative-free formulations,^{26,35,36} the current study further suggests that the dorzolamide–timolol preservative-free formulation may constitute an advantageous treatment alternative that provides a better tolerability for patients sensitive to preservative or for whom the utilization of preservative-free formulation is otherwise advisable.

Limitations of the current study relate to the open-label, single cohort design that did not include a comparative group. The study design was thus not amenable to answer some potentially interesting questions. For instance, recent observations from daily practice indicate that while most patients are satisfied with their medication, 9% of new users had their medication stopped by their ophthalmologist due to side effect.²⁸ Comparing the nonvisual symptoms between various treatments or between preserved and unpreserved formulations of dorzolamide–timolol would have been informative. However, the principal objective of the present study was to measure changes in eye comfort from baseline to 8 weeks of treatment with preservative-free dorzolamide–timolol formulation and not to perform between treatment group comparisons. By conducting within- instead of between-group comparison, all possible confounding bias related to disease and lifestyle factors that may affect IOP changes were avoided since each patient provided both control (pretreatment) and on treatment data.³⁷ Further, a blinded treatment regimen would not have been compatible with a clinical practice setting. The current single-cohort, open-label, prospective design was thus implemented in order to achieve study objectives and to more accurately reflect real-life clinical settings.

An important strength of this study is the generalizability of its results to the Canadian target population. This study was conducted in real-life clinical settings where physicians treated patients as per their clinical judgment within the constraints of their clinical practice. These characteristics thus better emulate the routine clinical practice and permit the assessment of real-life effectiveness and safety. In addition, the use of a standardized and validated questionnaire (the GSS)²⁴ to assess the ocular symptoms experienced by the patients enhances study validity.²⁴ Based on their baseline scores, patients enrolled in this study likely represent the patient population who would benefit from the preservative-free medication.

In conclusion, the results of this study conducted in a real-life setting demonstrated that preservative-free dorzolamide–timolol formulation does not increase eye discomfort while significantly reducing intra-ocular pressure in

treatment-naïve, newly diagnosed patients with open-angle glaucoma or ocular hypertension. Future real-life studies assessing the relative difference in nonvisual symptoms between various glaucoma treatments and between preserved and unpreserved formulations of dorzolamide–timolol, would further contribute to the management of glaucoma.

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Trial registration number: This study is registered at clinicaltrials.gov: NCT # 000545064.

Disclosures

C Hutnik, D Neima, F Ibrahim, and R Scott have no competing financial interests to declare. N Bastien and S Foucart are employees of Merck Frosst Canada Ltd; J Vaillancourt, D Haine, and J Sampalis are employees of JSS Medical Research Inc (contract research organization); all study investigators received grants related to the conduct of the study.

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