Clinical Ophthalmology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Maximum Tolerated Medical Therapy for Glaucoma: Fixed-Dose Combinations of Timolol, Dorzolamide, Brimonidine with Latanoprost Versus Timolol, Dorzolamide with Latanoprost

Oscar Olvera-Montaño[1], Claudia Mejia-Morales[1], Ricardo O Jauregui-Franco[1], Sandra Carolina Gomez-Mendez[1], Patricia Muñoz-Villegas[1,2]

[1]Regional Medical Affairs Department, Laboratorios Sophia, S.A. de C.V, Jalisco, Mexico; [2]Centro de Investigación en Matemáticas (CIMAT), Unidad, Aguascalientes, Aguascalientes, Mexico

Correspondence: Patricia Muñoz-Villegas, Laboratorios Sophia, S.A. de C.V, Paseo del Norte 5255, Guadalajara Technology Park, Zapopan, Jalisco, 45010, Mexico, Tel +52 33 3301 4200, Email patricia.munoz@sophia.com.mx

Purpose: Maximal medical therapy involves using three or more classes of topical anti-glaucoma agents to achieve the target intraocular pressure (IOP). This study compared the effectiveness, tolerability, and safety of a fixed combination of timolol, dorzolamide, brimonidine, and latanoprost (TDB-L) versus a fixed combination of timolol, dorzolamide, and latanoprost (TD-L) for uncontrolled IOP in patients with primary open-angle glaucoma.

Methods: In this randomized, double-masked Phase IV trial, 47 eyes from 26 patients were assigned to TDB-Lor TD-L for 60 days, with follow-ups on days 14, 30, and 60. IOP was measured at 9:00 and 11:00 a.m. Follow-ups assessed tolerability via the Ocular Comfort Index (OCI) and conjunctival hyperemia (CH). Safety evaluations included chemosis, fluorescein conjunctival staining (FCS), visual acuity, corneal and retinal nerve fiber layer thickness, ganglion cell layer, and adverse events (AEs).

Results: By day 60, both treatment groups achieved a significant reduction in IOP, with TDB-L decreasing from 20.1 ± 1.6 mmHg to 14.0 ± 2.2 mmHg and TD-L from 20.8 ± 1.8 mmHg to 16.8 ± 2.0 mmHg (between groups, $p = 0.042$). In the TDB-L group, the reduction in IOP by day 60 was 6.3 mmHg, compared to 4.5 mmHg in the TD-L group. OCI scores did not significantly change. By day 60, 15% of eyes exhibited moderate CH (all in TD-L, $p = 0.002$). The safety of both groups was similar, as neither presented drug-related AEs nor showed differences in safety parameters, with differences being found only in FCS (between groups, $p = 0.001$).

Conclusion: Both TDB-L and TD-L achieved significant IOP reductions after two months, were well tolerated, and safe. Adding a fourth hypotensive agent may offer an effective option for patients needing more IOP reduction beyond TD-L, highlighting their role in managing glaucoma in regions with high socioeconomic burdens and limited treatment access.

Trial Registration: ClinicalTrials.gov identifier NCT04702789, registered on 21 October 2019.

Keywords: open-angle glaucoma, safety, intraocular pressure, tolerability

Introduction

Glaucoma is a group of progressive optic neuropathies characterized by the loss of retinal ganglion cells and their axons.[1] POAG is the predominant subtype in Mexico and Latin America, contributing significantly to vision loss and severe visual impairment. It is often asymptomatic until advanced stages, when visual damage becomes irreversible.[2] POAG represents a significant socioeconomic burden in Mexico, with direct and indirect costs exceeding USD 1.144 billion annually. This highlights the need for more effective and accessible treatments.[3] Additionally, in Mexico, treatment may consume up to 61.5% of the monthly income of low-resource patients, limiting adherence and exacerbating disease progression.[2] Elevated intraocular pressure (IOP) is a well-known risk factor for the development and progression of glaucoma, and controlling IOP has been the primary goal of glaucoma

Received: 14 May 2025
Accepted: 28 July 2025
Published: 22 August 2025

treatment.[4–6] The decrease in IOP has been demonstrated to reduce the risk of conversion from ocular hypertension (OHT) to POAG by approximately 20% for every mmHg.[5–7] Despite advancements in surgical filtration treatments, implants, and laser procedures that enhance trabecular drainage, drug therapy remains the primary intervention for most patients with OHT and glaucoma. This treatment generally involves the topical application of hypotensive medication agents.[8]

Pharmacotherapy typically starts with a single hypotensive agent, often one of the first-line treatments, such as prostaglandin analogs (PGAs) or β-blockers. However, in many cases, using just one medication may not be enough to reach the target IOP or to prevent the progression of glaucoma.[9] This can be achieved by concurrently using two or more medications or a fixed combination (FC). The fixed combinations effectively lower IOP and offer several advantages over the separate administration of their active ingredients: 1) reduced costs, 2) simpler treatment regimens, 3) improved treatment adherence, and 4) decreased washout risk.[10–13] When the target IOP is not achieved, a third medication can be added to achieve Zimmerman's maximal medical therapy regimen of three drugs daily instillations.[14,15] FC of three drugs can broaden the horizon toward the new maximum tolerated medical therapy plan proposed by Sampaolesi, which included fixed triple therapy (timolol, dorzolamide, and brimonidine) plus a PGA.[16] In addition to showing an adequate safety and tolerability profile, the FC of 0.5% timolol, 2% dorzolamide, and 0.2% brimonidine (Krytantek Ofteno®, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico) has been demonstrated to be more effective than the FC of two ocular hypotensive agents: specifically, the FC of 0.5% timolol with 2% dorzolamide, and the FC of 0.5% timolol with 0.2% brimonidine, demonstrating a reduction of IOP by 42.3% and 28.4%, respectively.[17,18] Since 2007 in Mexico, and in more recent years in other Latin American countries such as Bolivia, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Panama, the Dominican Republic and Uruguay, Krytantek Ofteno® (Timolol 0.5% / Brimonidine 0.2% / Dorzolamide 2% in ophthalmic solution) is commercially available, its sustained presence in these markets reflects both successful regulatory approval and positive commercial acceptance within the ophthalmic community.[19]

MMT aims to enhance patients' chances of reaching the target IOP and slowing disease progression, thereby creating effective and tolerable therapies as alternatives to surgery. Each class of antihypertensive agents provides an additive effect; however, the reduction in IOP achieved by adding a drug is less than that obtained when it is used as initial therapy. Different regimens can be combined to optimize treatment. These may include fixed triple or double combinations, as well as monotherapy. For four hypotensive agents, options include using two double combinations, a triple combination plus monotherapy, or all four agents concurrently.[20]

We hypothesized that the fixed-dose combination of timolol, dorzolamide, and brimonidine with latanoprost (TDB-L) would show superior IOP reduction, enhanced tolerability, and a safety profile comparable to the fixed-dose combination of timolol and dorzolamide with latanoprost (TD-L) in patients with POAG and uncontrolled IOP. The objective of this study was to assess the efficacy, tolerability, and safety of a maximum tolerated medical therapy for glaucoma using an FC of timolol, dorzolamide, and brimonidine with latanoprost, compared to an FC of timolol and dorzolamide with latanoprost in patients with POAG and uncontrolled IOP, treated with either a PGA or a β-blocker.

Patients and Methods

Study Design

This prospective, multicenter, double-masked, Phase IV, randomized study (ClinicalTrials.gov registration number: NCT04702789, registered on October 21, 2019) was conducted at five sites in Mexico. The protocol and informed consent were performed in accordance with the principles of the Declaration of Helsinki (1964), the International Council for Harmonization guidelines, Good Clinical Practice, and current local legislation. The study was approved by the Research Committee, as well as the Research Ethics Committee and the Federal Commission for the Protection against Sanitary Risks in Mexico. The study population consisted of volunteer patients who met the inclusion criteria and signed the informed consent form to undergo all the procedures involved. Patients were recruited from February 2022 to October 2023.

Patients

Participants were assessed for eligibility during a screening visit scheduled 30 days before baseline, when their medical and ocular histories were obtained. If the patient fulfilled all the inclusion criteria and presented none of the exclusion criteria, they were eligible for enrollment. To be selected, patients were required to have a diagnosis of POAG, as defined by the American Academy of Ophthalmology's preferred practice pattern guidelines, or they were required to have ocular hypertension. They also needed to be uncontrolled by a PGA or a β-blocker for at least 30 days before the screening visit.[21] During the screening visit, they received latanoprost for approximately 30 days and needed to adhere to the medication at least 90%. To qualify for the study, participants must have an IOP measured using a Goldmann application tonometer of 19 mmHg or greater, but not exceeding 26 mmHg, in the study eye in the eligibility and basal visit. All patients must be at least 18 years old. Exclusion criteria included the following: for women of childbearing age, a birth control method was necessary since pregnancy, breastfeeding, or high childbearing potential without a birth control method before inclusion. Other exclusion criteria included having an anterior chamber angle of less than two on Shaffer's scale or the presence of peripheral anterior synechia in the study eye, currently being under treatment with any systemic ocular hypotensive drug, having a best corrected visual acuity (BCVA) worse than 20/200 in the study eye, severe loss of central visual field, a previous history of ocular trauma within the last six months, and contraindications to any medication used in the study like severe asthma or chronic obstructive pulmonary disease, 2nd or 3rd-degree atrioventricular block not controlled with a pacemaker, sinus bradycardia, chronic kidney disease, patients who require the use of monoamine oxidase inhibitors and patients treated with antidepressants that affect noradrenergic transmission. All specific selection criteria are outlined in Table S1.

Treatment and Evaluations

All of them were assigned to receive preservative-free ocular 0.005% latanoprost eye drops (GAAP Ofteno® PF, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico) once a day at 09:30 p.m. ± 15 minutes for 30 days in the study eye (washout period). After one month, patients who met the selection criteria in at least one eye were included in the study for efficacy evaluation. A total of 47 eyes were randomized 1:1 to the use of the FC of 0.5% timolol, 2% dorzolamide, and 0.2% brimonidine (Krytantek Ofteno® PF, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico) with 0.005% latanoprost (TDB-L group) or the FC of 0.5% timolol, and 2% dorzolamide (Eliptic Ofteno® PF, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico) with 0.005% latanoprost (TD-L group). Randomization numbers were generated and uniformly distributed using statistical software, and patients were allocated treatments from a central list of permuted blocks for each stratum. The labels on the bottles used in the study were covered to maintain masking, and identical packaging was utilized. The treatment assignment was also blinded throughout the study for all researchers, patients, and sponsoring team members. The fixed combinations were administered twice daily at 09:00 a.m. ± 10 minutes and 09:00 p.m. ± 10 minutes for 60 days, and the latanoprost was administered once daily at 09:30 p.m. ± 15 minutes for the same period. The study drug was discontinued if either the principal investigator or the patient decided that continuing was not in the patient's best interest, if the therapies assigned showed a lack of efficacy (less than a 20% decrease in IOP when a fixed combination was added to the treatment with latanoprost), or if a female patient became pregnant. The flow chart of study participants is shown in Figure 1.

Outcome Variables

The primary efficacy endpoint was the change in IOP from baseline to day 60 (final visit). The tolerability and safety endpoints included the ocular comfort index (OCI), conjunctival hyperemia (assessed by the Efron grading scale), presence of chemosis, fluorescein conjunctival staining (FCS) to detect epithelial defects by Oxford scale, central corneal thickness (CCT), retinal nerve fiber layer, ganglion cell layer, BCVA (LogMAR), and the incidence of adverse events (AEs). The OCI questionnaire was developed in 2007 by Johnson and Murphy for English speakers using Rasch analysis and has since been adapted for Chinese and Spanish languages, yielding results comparable to those of the original version.[22–26] Expected (listed versus unexpected) AE were analyzed, including their causality, and severity (mild, moderate, severe).[27,28] For each AE, the following information was collected: duration, frequency, clinical severity,

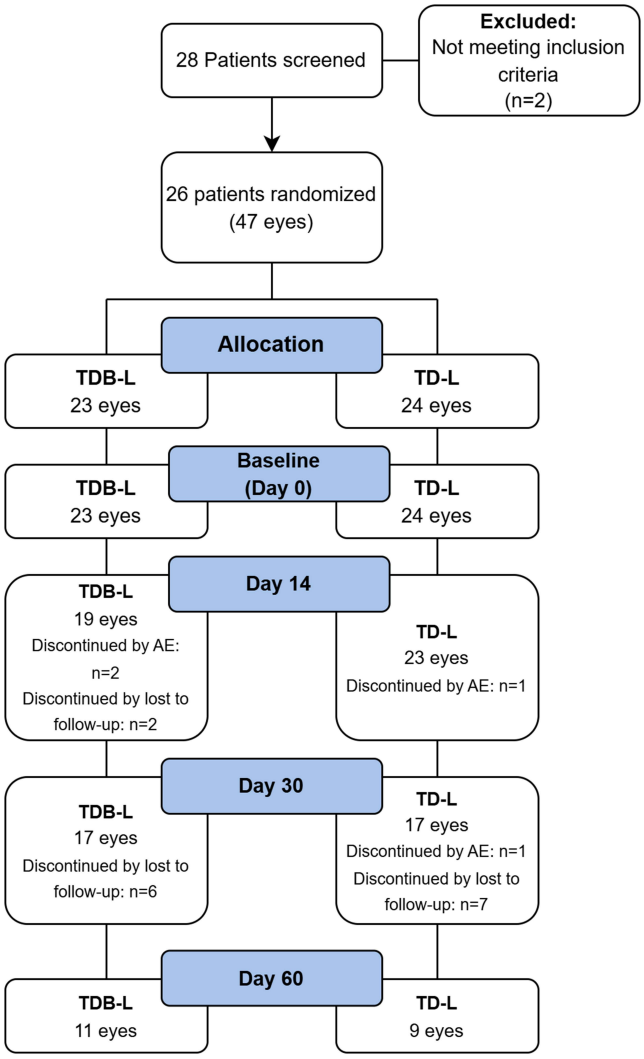

Figure 1 Current diagram of patients enrolled in the study.

relationship to therapy, action taken, and outcome. Causality assessment was based on the criteria of the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) to determine a possible association between the treatment and the observed reaction. All AEs occurring during the clinical protocol were recorded and included in the analysis.

A masked investigator measured IOP at identical times of day, with baseline examinations conducted at follow-up visits at 9:00 a.m. (before the morning dose) and 11:00 a.m., ± 30 minutes (two hours after morning dose). Follow-up visits were scheduled on days 14, 30, and 60 ± 2 after starting the therapy. The investigator ensured that the patient applied the therapy during treatment, following the 9:00 a.m. IOP check.

Statistical Analysis

Statistical analyses were carried out using the R statistical software (The R Foundation for Statistical Computing; http://www.R-project.org). Considering that the intent-to-treat (ITT) analysis population is the most clinically relevant and may better reflect real-world conditions, all participants were analyzed according to the groups to which they were randomized.[29,30] Before the study began, it was established that a minimum of 45 eyes per group was required to detect a difference of at least 1.5 mmHg in mean controlled IOP maintenance between treatments. This determination was based on a significance level of 0.05 and a desired power of 0.80.[31,32] Unfortunately, the study was terminated due to insufficient recruitment, which prevented the sample size from being reached. Since the sample collected was less

than 50% of the initially estimated amount needed for the superiority analysis, we did not conduct this analysis. Instead, we present all the results to illustrate the data we obtained. Continuous variables are characterized by the mean and standard deviation (SD). Pre- and post-treatment analyses were compared with a mixed-effect model, accounting for the intra-patient correlation to avoid overestimating significance and incorrect confidence intervals (CI) calculated at 95%. Ordinal variables were analyzed using p x q contingency tables, and depending on the analytical requirements, differences were calculated using Pearson's chi-squared test or Fisher's exact test. All statistical analyses in this study were two-sided, with a significance level of $p \leq 0.05$.

Results

Demographic Characteristics

The study included 47 eyes from 26 patients (9 male and 17 female), with a mean age ± SD of 67.3 ± 10.7 years (see Table 1). The mean BCVA (LogMAR) was 0.19 ± 0.19 for group TDB-L and 0.20 ± 0.19 for group TD-L; clinical signs, symptoms, and initial characteristics were similar, showing no significant differences. Patients in both groups exhibit a mean adherence of greater than 90% to the prescribed treatment during the washout period (data not shown). During the clinical follow-up, at day 14, adherence was 100 ± 0% vs 98.8 ± 2.9% for the TDB-L and TD-L groups, respectively. On day 30, it was 95.5 ± 12% vs 98 ± 4.5%, and on day 60, it was 91 ± 12.4% vs 99.3 ± 1.5%, without significant differences between arms (p = 0.327).

Efficacy

Intraocular Pressure Changes

As measured, IOP was significantly reduced in both groups at 9:00 a.m. The IOP decreased by 5.1 mmHg ($p < 0.0001$, 95% CI [−5.95, −4.58]), 6.2 mmHg ($p < 0.0001$, 95% CI [−7.01, −5.23]), and 6.2 mmHg ($p < 0.0001$, 95% CI [−6.27, −4.49]) after 14, 30, and 60 days of treatment (factor visit) compared to their baseline value. No differences were observed between groups at the baseline, day 14, and day 30 visits. But on day 60, the TDB-L group experienced a significant decrease at 9:00 a.m. compared to the TD-L group (p = 0.042, 95% CI [0.13, 3.64], Figure 2a).

At 11:00 a.m.(two hours after the morning dose), the IOP in both groups decreased by 4.1 mmHg ($p<0.0001$, 95% CI [−5.08, −3.07]), 5.7 mmHg ($p<0.0001$, 95% CI [−6.71, −4.62]), and 5.7 mmHg ($p<0.0001$, 95% CI [−6.90, −4.46]) after 14, 30, and 60 days of treatment, respectively, compared to their baseline values at this time. However, the IOP reduction

Table 1 Characteristics of Each Treatment Group

Variable		TDB-L	TD-L	p-value
No. of eyes		23	24	
Sex, M / F		33.3% / 66.7%	35.7% / 64.3%	0.899[a]
Age, years		63.0 ± 12.2	70.9 ± 7.9	0.058[b]
BMI, Kg/m^2		26.9 ± 4.23	27.4 ± 3.84	0.748[b]
BMI Categories	Healthful weight	41.7%	35.7%	0.883[a]
	Overweight	33.3%	42.9%	
	Obesity	25%	21%	
Use of concomitant medications		66%	92.9%	0.199[a]

Notes: For continuous variables, data are presented as mean ± standard deviation. groups. [a]chi-square test and [b]t-test are used. All p-values between groups are> 0.05.

Abbreviations: BMI, body mass index; F, female; M, male; TDB-L, fixed combination of timolol, dorzolamide, and brimonidine with latanoprost; TD-L, fixed combination of timolol, dorzolamide with latanoprost.

https://doi.org/10.2147/OPTH.S540312

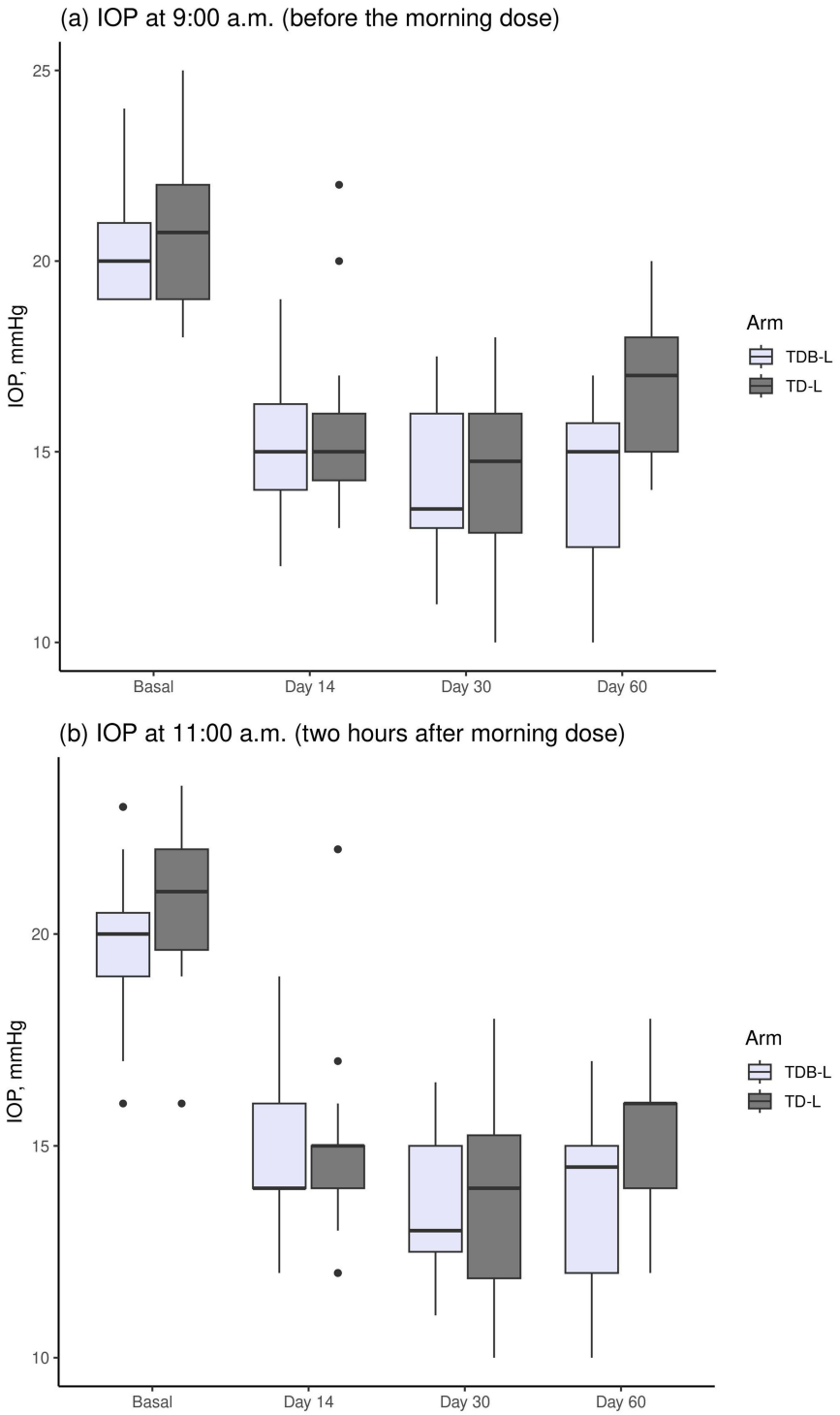

Figure 2 Mean intraocular pressure changes for TDB-L and TD-L treatments at each experimental visit at 9:00 a.m. (**a**) and 11:00 a.m. (**b**). Statistical significance was determined using a mixed-effects model. IOP reduction in TDB-L > TD-L on day 14 at 11:00 a.m. and day 60 at 9:00 a.m., *p <0.05.

was significantly observed only on day 14 for the TDB-L group versus TD-L (p = 0.034, 95% CI [−2.94, −0.15], Figure 2b). Figure 2 summarizes the IOP values for both groups at each time point.

The IOP measured at 11:00 a.m. in both groups was significantly lower than that measured at 9:00 a.m. in all visits (p = 0.004, 95% CI [−0.94, −0.18]). The plot of the estimated random effects for each eye and their confidence intervals is displayed in Figures S1 and S2.

The TDB-L group's baseline IOP value significantly decreased from 20.1 mmHg by 4.9 mmHg (p<0.0001, 95% CI [−5.86, −4.49]), 6.2 mmHg (p<0.0001, 95% CI [−7.18, −5.32]), and 6.3 mmHg (p<0.0001, 95% CI [−7.37, −5.20]) at days 14, 30, and 60, respectively. The difference between the 9:00 a.m. and 11:00 a.m. measurements was statistically significant (p = 0.006, 95% CI [−2.03, −0.35]).

In the TD-L group, the IOP decreased from 20.8 mmHg at baseline by 5.4 mmHg (p<0.0001, 95% CI [−6.36, −4.37]), 6.4 mmHg (p<0.0001, 95% CI [−7.51, −5.28]), and 4.5 mmHg (p<0.0001, 95% CI [−5.89, −3.13]) by days 14, 30, and 60, respectively. Remarkably, the IOP measured two hours after the morning dose was not significantly different from the values recorded at 9:00 a.m. (p=0.881).

Tolerability

Ocular Comfort Index

There were no differences in tolerability between the treatments, as assessed by the OCI score. The mean baseline OCI score was similar across therapies, at 33.2 ± 8.8 for the TDB-L group and 27.2 ± 8.7 for the TD-L group. The final OCI score on day 60 was 29.8 ± 17.6 for TDB-L, compared to 23.6 ± 15.6 for TD-L. Throughout all clinical follow-ups, the OCI scores did not show significant changes from baseline to day 60, as indicated in Table 2, nor during the other visits in either group (p-values of 0.344, 0.616, 0.602, and 0.451 at baseline, day 14, day 30, and day 60, respectively), as shown in Figure S3.

Table 2 Change From Baseline at Day 60 Follow-up

Variable	Visit	TDB-L	TD-L	p-value
IOP at 9:00 a.m., mmHg	Basal	20.1 ± 1.6	20.8 ± 1.8	0.042[a]
	Day 60	14.0 ± 2.2	16.8 ± 2.0	
IOP at 11:00 a.m., mmHg	Basal	19.2 ± 2.9	20.7 ± 1.7	0.443[a]
	Day 60	13.6 ± 2.1	15.1 ± 1.8	
BCVA, LogMAR	Basal	0.19 ± 0.19	0.20 ± 0.19	0.971[a]
	Day 60	0.12 ± 0.14	0.21 ± 0.22	
CCT, µm	Basal	554 ± 55.2	537 ± 33.5	0.688[a]
	Day 60	555 ± 52.1	533 ± 29.4	
Ganglion cell layer	Basal	79.6 ± 14.9	69.8 ± 3.20	0.463[a]
	Day 60	79.1 ± 15.0	72.0 ± 10.4	
Retinal nerve fiber layer	Basal	81.8 ± 12.4	71.6 ± 11.3	0.326[a]
	Day 60	79.9 ± 11.3	72.4 ± 11.8	
CH, Normal	Basal	33.3%	13%	0.002[b]
	Day 60	36.4%	22.2%	
FCS, grade 0	Basal	50%	30.4%	0.001[b]
	Day 60	81.8%	44.4%	
OCI, score	Basal	33.2 ± 8.8	27.2 ± 8.7	0.451[a]
	Day 60	29.8 ± 17.6	23.6 ± 15.6	

Notes: For continuous variables, data are presented as mean ± standard deviation. [a] mixed-effect model, [b] Chi-square test. All p-values indicate the comparison between arms at day 60.
Abbreviations: BCVA, best-corrected visual acuity; CCT, central corneal thickness; CH, conjunctival hyperemia; FCS, fluorescein conjunctival staining; IOP, intraocular pressure; OCI, ocular comfort index; TDB-L, fixed combination of timolol, dorzolamide, and brimonidine with latanoprost; TD-L, fixed combination of timolol, dorzolamide with latanoprost.

https://doi.org/10.2147/OPTH.S540312

Conjunctival Hyperemia

Based on the Efron scale, conjunctival hyperemia was scored from 0 (normal) to 4 (severe). At baseline, 22% of all eyes showed normal grading (33.3% vs 13% for the TDB-L and TD-L groups, respectively), while 70.8% had grades ranging from trace to mild (61.1% vs 78.3%). In comparison, 7.3% exhibited moderate hyperemia (5.6% vs 8.7%), p = 0.464. By day 60, 30% of all eyes had a normal score (36.4% and 22.2% for TDB-L and TD-L groups, respectively), with 55% having grades from trace to mild. The incidence of conjunctival hyperemia decreased to 55% for grades from trace to mild (63.6% vs 44.4%) but increased to 15% for moderate cases, p = 0.002. All cases of moderate hyperemia were noted in the eyes assigned to the TD-L group. No cases of severe hyperemia were recorded. See Table 2 and Figure S4.

Safety

Chemosis

No cases of chemosis were observed in any patients before or after their respective treatment.

Fluorescein Conjunctival Staining (FCS)

Compared to the baseline, both groups had an increase in the proportion of eyes with grade 0. At day 60, the proportion of eyes with grade 0 FCS increased from 50% to 81.8% in the TDB-L group, representing a relative improvement of 63.6%. In contrast, the TD-L group showed a smaller increase from 30.4% to 44.4% (a relative change of 46.1%). These changes were statistically significant (p = 0.001), see Table 2

Central Corneal Thickness (CCT), Retinal Nerve Fiber Layer, and Ganglion Cell Layer

No differences were observed in CCT between treatments (p = 0.688) at day 60 (p = 0.769), for retinal nerve fiber layers (factor group: p = 0.326, factor visit: p = 0.596), or the ganglion cell layer (factor group: p = 0.463, factor visit: p = 0.721), as shown in Table 2.

Best-Corrected Visual Acuity

Regarding the BCVA, no significant differences in mean values were observed at baseline (p = 0.814), day 14 (0.18 ± 0.18 vs 0.16 ± 0.16, p = 0.146), day 30 (0.18 ± 0.18 vs 0.14 ± 0.13, p = 0.281), or day 60 (0.12 ± 0.14 vs 0.21 ± 0.22, p = 0.840). Additionally, no significant differences were observed between groups (p = 0.971), as shown in Table 2 and Figure S5.

Adverse Events

Regardless of adverse event (AE) incidence, in the intention-to-treat (ITT) analysis involving 26 patients, 76.9% (20/26) reported at least one AE, resulting in 75 AE occurrences (32 in the TDB-L group and 43 in the TD-L group), as shown in Table 3. Among these, 26.7% were classified as unexpected-AE. 6.3% of all AEs were associated with the TDB-L group, while 41.9% were reported in the TD-L group (p < 0.001, Chi-square test).

Table 3 Treatment-Related Adverse Events

		TDB-L	TD-L
Patients with AE, n (%)		9 (75)	11 (78.6)
Unexpected / Expected-AE, n (%)		2 (6.3) / 30 (93.8)	18 (41.9) * / 25 (58.1)
Severity, n (%)	Mild	29 (90.6)	41 (95.3)
	Moderate	3 (9.4)	2 (4.7)
	Severe	0	0

(*Continued*)

Table 3 (Continued).

		TDB-L	TD-L
Causality, n (%)	Possible	5 (15.6)	8 (18.6)
	Probable or likely	9 (28.1)	7 (16.3)
	Unlikely	18 (56.2)	28 (65.1)
Non-ocular AE, n (%)		8 (25)	4 (9.3)
Ocular AE, n (%)		24 (75)	39 (94.1)
Installation site irritation, n (%)		5 (20.8)	5 (12.8)
Foreign body sensation, n (%)		1 (4.2)	5 (12.8)
Pruritus, n (%)		2 (8.3)	4 (10.3)
Eye irritation, n (%)		2 (8.3)	4 (10.3)
Other, n (%)		14 (58.4)	21 (53.8)
Total, AE, n (%)		32 (42.7)	43 (57.3)

Notes: The data indicate frequency (percentage), n = 26 randomized patients. Of the total adverse events (AEs), 26.7% were unexpected AEs, 6.3% were associated AEs from TDB-L, and 41.9% were reported by the TD-L group (*p < 0.001, Chi-square test).
Abbreviations: AE, adverse event; TDB-L, timolol-dorzolamide-brimonidine with latanoprost; TD-L, timolol-dorzolamide with latanoprost.

In terms of severity, 90.6% of the adverse events (AEs) in the TDB-L group were classified as mild, while 9.4% were moderate, comprising one case each of dry eye, headache, and gastrointestinal infection. For the TD-L group, 95.3% of AEs were mild, and 4.7% were moderate, consisting of one case of iridocyclitis and one of conjunctivitis (p = 0.417, Chi-square test). No severe AEs occurred during the study. Regardless of their causality, 17.3% of adverse events (AEs) were deemed possible, 21.3% were classified as probable or likely, and 61.3% were considered unlikely (p = 0.464 between groups, see Figure S6). The most reported AE was irritation at the instillation site (13.3%), followed by pruritus and a foreign body sensation (8.0%).

Discussion

Has been reported that approximately 40% of patients in the Ocular Hypertension Treatment Study required multiple medications to achieve a 20% IOP reduction.[33,34] Although PGAs are the most used medications, many physicians consider β-blockers the preferred adjunctive therapy alongside PGAs (intermediate therapy).[17,35] However, there are cases where intermediate therapy or the beginning of treatment requires a significant decrease in IOP. In these situations, the tolerated MMT can be considered. MMT uses three or more anti-glaucoma agents.[15] This study demonstrated that the use of timolol, dorzolamide, and brimonidine twice daily for 60 days, as an adjunct to latanoprost administered once daily, provided a clinically meaningful IOP reduction in patients with POAG who were inadequately controlled on intermediate therapy. Our findings show that patients assigned to four hypotensive agents or to double FC with monotherapy experienced a significant decrease in IOP from 20 mmHg to 14 mmHg by day 60 for the triple FC, including latanoprost, and from 21 mmHg to 17 mmHg with the double FC plus latanoprost. These changes correspond to a decrease from 31.4% for the TDB-L group and 19.6% for the TD-L group before the morning dose. IOP fluctuates throughout the day and typically peaks at night. Large fluctuations in IOP may increase the risk of progression in glaucoma.[36] IOP can fluctuate due to autonomic or humoral control, changes in vascular tone, and changes in bodily posture.

Before suggesting a four-drug combination, verifying the efficacy of adding a fourth medication to a patient's medical regimen is important.[20] It has been reported that 20% of patients who received a four-drug combination experienced an

increase in IOP of 20% or more after undergoing a washout of the fourth drug. In a retrospective study, Bro et al, investigated the effects of adding brimonidine as the fourth drug. Patients followed for one to 12 months showed a decrease in IOP of 20% or more.[37] Hence, although the literature is scarce, adding a fourth drug appears clinically helpful in 20% to 50% of patient cases.[20,37,38] Previously, a fourth medication was not used, as the patient had to apply numerous drops, which could reduce their adherence. However, incorporating a triple FC, such as timolol, dorzolamide, and brimonidine, simplifies treatment by adding a PGA, thereby creating a new maximum tolerated medical therapy regimen option for glaucoma.[16]

The degree of ocular tolerability is a crucial determinant of compliance with the dosing regimen for any ophthalmic medication, including glaucoma therapies, and has a direct impact on treatment efficacy.[39,40] In our study, all patients demonstrated an adherence rate greater than 90% to their prescribed treatment throughout the clinical follow-up period. Insufficient adherence to therapy among patients with glaucoma is a prevalent issue that poses significant health, social, and economic challenges. Poor adherence is associated with disease progression, increased complication rates, and higher healthcare costs.[40,41]

The combination of timolol, dorzolamide, and brimonidine with latanoprost and the TD-L was well tolerated, as indicated by similar OCI scores between groups from baseline to day 60. Glaucoma is often associated with ocular surface disease, making the topical therapy burden a predictor of corneal staining severity. Glaucoma treatment may cause chronic inflammation or aggravate a concomitant ocular surface disease. Patients may also have preexisting ocular surface diseases, dry eye syndrome, meibomian gland dysfunction, or chronic allergies. Some ocular surface issues can worsen when patients are treated with more than one topical glaucoma medication.[42–44] Benzalkonium chloride (BAK) is the most used preservative in topical drugs, with evidence indicating toxic effects on ocular tissues.[44,45] In our study, the final OCI score ranged from 0 to 51 points for both treatments, similar to those observed during the screening visit (0 to 52 points, respectively). This may be attributed to the use of preservative-free (BAK-free) medications, and the shorter treatment duration is also expected to enhance the favorable tolerability of the therapies.

Ocular hyperemia is the most common side effect of topical hypotensive medications.[46] By day 60, conjunctival hyperemia generally improved, though moderate cases increased to 15% in the TD-L group. No severe cases were observed. Yanagi et al reported higher hyperemia in patients treated with prostaglandin compared to those treated with β-blockers or no eye drops. The study excluded patients who had been on glaucoma treatment for less than six months.[46] In agreement with our findings, conjunctival hyperemia appeared stable in all patients. All hypotensive agents used in this study were BAK-free, which is reported to induce less conjunctival inflammation than BAK eye drops.

CCT is a crucial variable in glaucoma; however, measurements vary by race, sex, and other environmental factors, which may complicate the relationship between glaucoma and central thickness.[47] Changes in CCT following the use of two or more glaucoma drug therapies can be observed within the first 1 to 2 years of treatment.[48] In our study, on the final visit, there was no statistical significance in the CCT between the TDB-L and TD-L groups or compared to the baseline value (after the washout period with a PGA), a result that was expected due to the short follow-up period. Additionally, the use of different devices to determine CCT has resulted in variable measurements. Considering these factors, our results align with those of previous similar studies, which have also noted variability between subjects.[47,49] Changes in the optic nerve head reflect the activity of retinal ganglion cell axons. The retinal nerve fiber and ganglion cell layers showed minimal, non-significant changes, likely due to small sample size and follow-up duration.

The occurrence of AEs in both groups appeared consistent with the established safety profiles of the individual hypotensive agents. Indeed, the only difference between the two treatments was the occurrence of unexpected AEs, which were reported in 6.3% of the TDB-L group compared to 41.9% of the TD-L group. The most frequently reported AE was irritation at the instillation site, followed by pruritus and foreign body sensation. These are expected AE related to glaucoma eye drops, and do not entail any additional safety risk associated with the formulations employed in this study.[17,35,50–53] Also, severe AE did not occur during the study follow-up. Our findings support the potential benefit of adding a fourth hypotensive agent to an MMT regimen to achieve more ambitious therapeutic goals in patients with suboptimal pressure (IOP) control.

Our current study has several potential limitations. First, the small sample size (n = 47 eyes) may affect the statistical power and generalizability of our findings. Initially, we conceived this study under a superiority hypothesis.

Unfortunately, the study was terminated due to insufficient recruitment, as the investigation sites faced challenges related to COVID-19 pandemic restrictions and strict selection criteria, among other factors. To illustrate the results of the data obtained while discarding the original superiority analysis, we utilized a mixed-effects model that accounted for adjusted intra-patient correlation. This statistical approach reduced the risk of drawing incorrect conclusions from the data. Second, the short-term study did not permit a long-term assessment of the efficacy and safety parameters of the treatments.[54] However, previous studies have reported the efficacy and safety of TDB, TD, and their active ingredients for up to six months.[17,18] Lastly, the study focused exclusively on patients with primary open-angle glaucoma, making the results inapplicable to other forms of glaucoma, such as angle-closure or congenital glaucoma.[2] However, one of the reasons this group of patients was chosen is that the Latin American population, especially those of Mexican descent, is more prone to developing POAG compared to Anglo-Saxons.[55,56] In summary, this study highlights the potential of using fixed combinations to simplify maximal medical therapy regimens, achieving effective IOP control with fewer medications and maintaining safety and tolerability. Such simplification may favor adherence and reduce treatment burden in clinical practice.

Conclusion

In conclusion, TDB-L and TD-L, as the MMT, demonstrate clinically relevant reductions in IOP for patients with POAG after two months of treatment. Both therapies were well tolerated, and the adverse events aligned with the known safety profiles of the individual medications. Adding a fourth hypotensive agent may offer an effective treatment option for patients needing additional IOP reduction beyond what is achieved with TD-L. These findings are particularly relevant for clinicians managing this disease in Latin America, where the socioeconomic burden is high and access to pharmacological treatments may be limited.

Abbreviations

AE, adverse events; BCVA, best-corrected visual acuity; FCS, fluorescein conjunctival staining; IOP, intraocular pressure; MMT, maximal medical therapy; OCI, ocular comfort index; PGA, Prostaglandin analog; POAG, primary open-angle glaucoma; TDB-L, fixed combination of timolol, dorzolamide, and brimonidine with latanoprost; TD-L, fixed combination of timolol, dorzolamide with latanoprost.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments

The study protocol and informed consent form were approved by their respective Institutional Review Boards as follows: *Hospital Universitario Dr. José Eleuterio González, Hospital La Misión, Asociación para Evitar la Ceguera en México, Clínica de Enfermedades Crónicas y de Procedimientos Especiales*, and *Centro Integral Médico SJR*. The authors would like to thank the staff of the following research sites for their support in conducting this study: *Departamento de Oftalmología, Hospital Universitario* "Dr. José Eleuterio González", *Servicios Médicos y de Investigación Clínica Inspire Pharma R.L de C.V, Asociación para Evitar la Ceguera APEC, Global Glaucoma Institute*, and *Consultorio de Oftalmología.*

We thank the participants in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Laboratorios Sophia, S.A. de C.V. (Zapopan, Jalisco, México) endorsed this study. The funder provided support in salaries for the authors [OOM, CMM, ROJF, SCGM, PMV], but this commercial affiliation did not play an additional role in data collection. The institutions associated with the Study Group's members received funds from Laboratorios Sophia, S.A. de C.V.

Disclosure

OOM, CMM, ROJF, SCGM, and PMV are employees of Laboratorios Sophia, S.A. de C.V. The authors report no other conflict of interest in this work.

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004;363(9422):1711–1720. doi:10.1016/S0140-6736(04)16257-0
2. Barría von-Bischhoffshausen F, Jiménez-Román J. Guía latinoamericana de glaucoma primario de ángulo abierto. 2019.
3. García Luna E, Guerrero AS. Socioeconomic impact of primary open angle glaucoma in mexico. *J Clin Exp Ophthalmol*. 2016;07(04). doi:10.4172/2155-9570.1000575
4. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R. Intraocular pressure control and long-term visual field loss in the collaborative initial glaucoma treatment study. *Ophthalmology*. 2011;118(9):1766–1773. doi:10.1016/j.ophtha.2011.01.047
5. Kass MA. The ocular hypertension treatment study. *Archives of Ophthalmol*. 2002;120(6):701. doi:10.1001/archopht.120.6.701
6. Chauhan BC. Canadian glaucoma study. *Archives of Ophthalmol*. 2008;126(8):1030. doi:10.1001/archopht.126.8.1030
7. Leske MC. Factors for glaucoma progression and the effect of treatment. *Archives of Ophthalmol*. 2003;121(1):48. doi:10.1001/archopht.121.1.48
8. Markus C, Bhagat P, K VKS, et al. Efficacy and safety of benzalkonium chloride-free fixed-dose combination of latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2014:1241.
9. Aung T, Sharma S, Trikha S, Perera S. Clinical effectiveness of brinzolamide 1%–brimonidine 0.2% fixed combination for primary open-angle glaucoma and ocular hypertension. *Clin Ophthalmol*. doi:10.2147/OPTH.S72380
10. Lazcano-Gomez G, Hernandez-Oteyza A, Iriarte-Barbosa MJ, Hernandez-Garciadiego C. Topical glaucoma therapy cost in Mexico. *Int Ophthalmol*. 2014;34(2):241–249. doi:10.1007/s10792-013-9823-6
11. Higginbotham EJ. considerations in glaucoma therapy: fixed combinations versus their component medications. *Clin Ophthalmol*. 2010;4:1–9.
12. Holló G, Topouzis F, Fechtner RD. Fixed-combination intraocular pressure-lowering therapy for glaucoma and ocular hypertension: advantages in clinical practice. *Expert Opin Pharmacother*. 2014;15(12):1737–1747. doi:10.1517/14656566.2014.936850
13. Babic N. Fixed combinations of glaucoma medications. *Srp Arh Celok Lek*. 2015;143(9–10):626–631. doi:10.2298/SARH1510626B
14. Zimmerman TJ. Maximal medical therapy for glaucoma. *Archives of Ophthalmol*. 1997;115(12):1579. doi:10.1001/archopht.1997.01100160749014
15. Lerner SF, Oddone F, Lu DW, et al. Maximum medical therapy: brinzolamide/brimonidine and travoprost/timolol fixed-dose combinations in glaucoma and ocular hypertension. *Clin Ophthalmol*. 2019;13:2411–2419. doi:10.2147/OPTH.S228777
16. Sampaolesi R, Sampaolesi JR, Zárate J. *The Glaucomas*. Berlin Heidelberg: Springer; 2014. doi:10.1007/978-3-642-35500-4
17. Baiza-Durán LM, Llamas-Moreno JF, Ayala-Barajas C, Gonzalez-Lomeli M. Comparison of timolol 0.5% + brimonidine 0.2% + dorzolamide 2% versus timolol 0.5% + brimonidine 0.2% in a Mexican population with primary open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. doi:10.2147/OPTH.S33578
18. Baiza-Durán LM, Alvarez-Delgado J, Contreras-Rubio AY, et al. The efficacy and safety of two fixed combinations: timolol-dorzolamide-brimonidine versus timolol-dorzolamide. A prospective, randomized, double-masked, multi-center, 6-month clinical trial. *Ann Ophthalmol*. 2009;41(3–4):174–178.
19. Olvera-Montaño O. Safety and tolerability of the preservative-free ophthalmic solution PRO-122 compared with krytantek ofteno® (PRO-122/I) (ClinicalTrials.gov: NCT03966365). Available from: https://clinicaltrials.gov/study/NCT03966365?term=NCT03966365&rank=1. Accessed August 18, 2025.
20. Costa VP, Aung T, Konstas AG. Evolution of the treatment paradigm for maximum medical therapy in glaucoma. *Expert Rev Ophthalmol*. 2019;14(1):33–42. doi:10.1080/17469899.2019.1570138
21. Gedde SJ, Vinod K, Wright MM, et al. Primary open-angle glaucoma preferred practice pattern®. *Ophthalmology*. 2021;128(1):P71–P150. doi:10.1016/j.ophtha.2020.10.022
22. Johnson ME, Murphy PJ. Measurement of ocular surface irritation on a linear interval scale with the ocular comfort index. *Investigat Opthalmol Vis Sci*. 2007;48(10):4451. doi:10.1167/iovs.06-1253
23. Okumura Y, Inomata T, Iwata N, et al. A review of dry eye questionnaires: measuring patient-reported outcomes and health-related quality of life. *Diagnostics*. 2020;10(8):559. doi:10.3390/diagnostics10080559
24. McAlinden C, Gao R, Wang Q, et al. Rasch analysis of three dry eye questionnaires and correlates with objective clinical tests. *Ocul Surf*. 2017;15(2):202–210. doi:10.1016/j.jtos.2017.01.005
25. Chao C, Golebiowski B, Cui Y, Stapleton F. Development of a Chinese Version of the ocular comfort index. *Investigat Opthalmol Vis Sci*. 2014;55(6):3562. doi:10.1167/iovs.14-14276
26. Barrio AR, González-Pérez M, Heredia-Pastor C, Enríquez-Fuentes J, Antona B. Spanish cross-cultural adaptation, Rasch analysis and validation of the Ocular Comfort Index (OCI) questionnaire. *Int J Environ Res Public Health*. 2022;19(22):15142. doi:10.3390/ijerph192215142
27. Dang TT, Nguyen TH, Ho TB. Causality assessment of adverse drug reaction: controlling confounding induced by polypharmacy. *Curr Pharm Des*. 2019;25(10):1134–1143. doi:10.2174/1381612825666190416115714
28. WHO-UMC. The Use of the WHO-UMC system for standardised case causality assessment. Available from: https://www.who.int/publications/m/item/WHO-causality-assessment. Accessed August 18, 2025.

29. DeSouza CM, Legedza ATR, Sankoh AJ. An overview of practical approaches for handling missing data in clinical trials. *J Biopharm Stat*. 2009;19(6):1055–1073. doi:10.1080/10543400903242795
30. Streiner D, Geddes J. Intention to treat analysis in clinical trials when there are missing data. *Evid Based Ment Health*. 2001;4(3):70–71. doi:10.1136/ebmh.4.3.70
31. Joh HJ, Jin SW. Comparison of different combinations of maximum medical therapy for lowering intraocular pressure in primary open angle glaucoma: 12-month retrospective consecutive case series. *Jpn J Ophthalmol*. 2019;63(4):322–327. doi:10.1007/s10384-019-00673-8
32. Chow SC, Wang H, Shao J. *Sample Size Calculations in Clinical Research*. Chapman and Hall/CRC; 2007; doi:10.1201/9781584889830
33. Wang CY, Chen YY, Liu CJL. Assessing the safety and efficacy of switching to brinzolamide/timolol fixed combination as a replacement therapy in patients with uncontrolled intraocular pressure in Taiwan. *Taiwan J Ophthalmol*. 2012;2(3):85–88. doi:10.1016/j.tjo.2012.08.001
34. Radcliffe N. The impact of timolol maleate on the ocular tolerability of fixed-combination glaucoma therapies. *Clin Ophthalmol*. doi:10.2147/OPTH.S76053
35. O'Connor DJ, Martone JF, Mead A. Additive intraocular pressure lowering effect of various medications with latanoprost. *Am J Ophthalmol*. 2002;133(6):836–837. doi:10.1016/S0002-9394(02)01418-6
36. Huang A, Mai A, Goldberg J, et al. The benefit of nocturnal IOP reduction in glaucoma, including normal tension glaucoma. *Clin Ophthalmol*. 2024;18:3153–3160. doi:10.2147/OPTH.S494949
37. Bro T, Lindén C. The more, the better? the usefulness of brimonidine as the fourth antiglaucoma eye drop. *J Glaucoma*. 2018;27(7):643–646. doi:10.1097/IJG.0000000000000987
38. Juncal VR, Abdo Jorge F, Paranhos A, Santos Prata T. Carbonic anhydrase inhibitors as fourth drug in primary glaucomas: is it worth it? *Can J Ophthalmol*. 2015;50(4):297–301. doi:10.1016/j.jcjo.2015.03.009
39. Mundorf T, Wilcox KA, Ousler GW, Welch D, Abelson MB. Evaluation of the comfort of Alphagan® P compared with Alphagan® in irritated eyes. *Adv Ther*. 2003;20(6):329–336. doi:10.1007/BF02849799
40. Muñoz-Villegas P, Martínez-Bautista H, Olvera-Montaño O. Determinants of adherence to treatment in patients with ophthalmic conditions. *Expert Rev Clin Pharmacol*. 2023;16(12):1249–1259. doi:10.1080/17512433.2023.2279740
41. Quaranta L, Novella A, Tettamanti M, Pasina L, Weinreb RN, Nobili A. Adherence and persistence to medical therapy in glaucoma: an overview. *Ophthalmol Ther*. 2023;12(5):2227–2240. doi:10.1007/s40123-023-00730-z
42. Scelfo C, ElSheikh RH, Shamim MM, Abbasian J, Ghaffarieh A, Elhusseiny AM. Ocular surface disease in glaucoma patients. *Curr Eye Res*. 2023;48(3):219–230. doi:10.1080/02713683.2022.2041041
43. Srivastava K, Bhatnagar KR, Shakrawal J, et al. Ocular surface changes in primary open-angle glaucoma on anti-glaucoma medications versus treatment-naïve patients. *Indian J Ophthalmol*. 2024;72(3):374–380. doi:10.4103/IJO.IJO_618_23
44. Villani E, Sacchi M, Magnani F, et al. The ocular surface in medically controlled glaucoma: an in vivo confocal study. *Investigat Opthalmol Vis Sci*. 2016;57(3):1003. doi:10.1167/iovs.15-17455
45. Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. *Drugs Aging*. 2011;28(4):267–282. doi:10.2165/11588830-000000000-00000
46. Yanagi M, Kiuchi Y, Yuasa Y, et al. Association between glaucoma eye drops and hyperemia. *Jpn J Ophthalmol*. 2016;60(2):72–77. doi:10.1007/s10384-016-0426-4
47. Sng CCA, Ang M, Barton K. Central corneal thickness in glaucoma. *Curr Opin Ophthalmol*. 2017;28(2):120–126. doi:10.1097/ICU.0000000000000335
48. Belovay GW, Goldberg I. The thick and thin of the central corneal thickness in glaucoma. *Eye*. 2018;32(5):915–923. doi:10.1038/s41433-018-0033-3
49. Hahn S, Azen S, Ying-Lai M, Varma R. Central corneal thickness in latinos. *Investigat Opthalmol Vis Sci*. 2003;44(4):1508. doi:10.1167/iovs.02-0641
50. Cheng JW, Li Y, Wei RL. Systematic review of intraocular pressure-lowering effects of adjunctive medications added to latanoprost. *Ophthalmic Res*. 2009;42(2):99–105. doi:10.1159/000225963
51. Yang XT. Efficacy and safety of 0.0015% tafluprost versus 0.005% latanoprost in primary open angle glaucoma, ocular hypertension: a Meta-analysis. *Int J Ophthalmol*. 2020;13(3):474–480. doi:10.18240/ijo.2020.03.16
52. Gómez-Aguayo F, Paczka JA, Leñero-Córdova R, et al. A Phase III Randomized Clinical Trial of a 0.5% Timolol + 0.2% Brimonidine + 2.0% Dorzolamide Fixed Combination, Preservative-Free Ophthalmic Solution vs. 0.5% Timolol + 0.2% Brimonidine + 2.0% Dorzolamide Fixed Combination in Patients with Controlled Primary Open-Angle Glaucoma. *Ophthalmol Ther*. 2018;7(1):145–156. doi:10.1007/s40123-018-0128-8
53. Sanchez-Castellanos VE, Paczka JA, Gomez-Aguayo F, et al. A Phase III, randomized, clinical, crossover study to evaluate the non-inferiority of an ophthalmic solution of preservative-free latanoprost at 0.005% in patients with primary open-angle glaucoma. *New Front Ophthalmol*. 2018;4(3). doi:10.15761/NFO.1000202
54. Menon MG, Goodkin ML. triple fixed-combination bimatoprost/brimonidine/timolol in glaucoma and ocular hypertension in India: a multicenter, open-label, phase 3 study. *Clin Ophthalmol*. 2022;16:3559–3569. doi:10.2147/OPTH.S369626
55. Kim E, Varma R. Glaucoma in Latinos/Hispanics. *Curr Opin Ophthalmol*. 2010;21(2):100–105. doi:10.1097/ICU.0b013e3283360b1e
56. Varma R, Wang D, Wu C, et al. Four-year incidence of open-angle glaucoma and ocular hypertension: the Los angeles latino eye study. *Am J Ophthalmol*. 2012;154(2):315–325.e1. doi:10.1016/j.ajo.2012.02.014