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ABOGADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

Ref: EXPEDIENTE No. 12-122166

Solicitud de patente a nombre de

ALLERGAN, INC.

Asunto: Recurso de Reposición

Por el presente me permito manifestar que interpongo Recurso de Reposición contra la resolución No. 61404 de fecha 14 de Octubre de 2014, por medio de la cual su Despacho denegó la patente de invención para la creación titulada COMBINACION TRIPLE PARA REDUCIR LA PRESION INTRAOCULAR, que se tramita en el Expediente mencionado en la referencia.

Al mismo tiempo, y en el artículo primero declaro fundadas las oposiciones presentadas por las sociedades Tecnoquimicas S.A. y Laboratorio Franco Colombiano- Lafrancol S.A.S.

La Resolución recurrida concluye que las reivindicaciones 1 a 13 no cumplen con el requisito de nivel inventivo, debido a los argumentos que se discuten a continuación:

I. **La Resolución 61404 concluye que D1 y D2 motivan al experto en la materia a preparar una composición conteniendo bimatoprost, brimonidina y timolol.**

Frente a tal argumento y con el fin de demostrar la existencia del nivel inventivo en la composición de interés de mi representada, se realizan las siguientes apreciaciones de cara a la pertinencia de las sugerencias divulgadas por D1 y D2:

1. D1[1] resuelve un problema técnico diferente al propuesto por la solicitud Colombiana CO 12-122-166, pues realiza un estudio para evaluar la tolerancia y la eficiencia entre dos combinaciones de fármacos. Más específicamente, el fin de D1 es comparar dos combinaciones de activos: brimonidina-timolol y dorzolamida-timolol:

   The objective of this study was to evaluate the IOP-lowering efficacy and ocular tolerability of ***brimonidine-timolol*** *compared with* ***dorzolamide-timolol*** *when used as monotherapy or as adjunctive therapy to a prostaglandin analog (PGA) in patients with glaucoma or ocular hypertension.*

   Por lo tanto, D1 no puede considerarse como "*el documento más cercano a la solicitud*" pues no se enfoca en el mismo problema técnico de la invención descrita en el expediente CO 12-122-166 y de ninguna manera sugiere al experto en la materia a combinar tres principios activos útiles para tratar la Presion Intra Ocular (PIO) entre los cuales se encuentre brimonidina, timolol y bimatoprost.

[1] http://informahealthcare.com/doi/abs/10.1185/03007990902994041

Efectivamente el documento cita: "***brimonidine-timolol*** *compared with* ***dorzolamide-timolol*** *when used as monotherapy or as adjunctive therapy to a prostaglandin analog (PGA)",* pero no enseña o sugiere cuál análogo de prostaglandina (en adelante PGA) puede brindar una mejora en la seguridad del uso de tal medicamento:

*In all, 180 patients with open-angle glaucoma or ocular hypertension who were in need of lower IOP received topical brimonidine-timolol BID or dorzolamide-timolol BID as monotherapy (n = 101) or as adjunctive therapy to a PGA (**latanoprost, bimatoprost, or travoprost**) (n = 79).*

Como se observa en el extracto anterior, D1 enseña que algunas PGA's empleadas para tratar la PIO podrían ser latanoprost, bimatoprost, y travoprost. Sin embargo, D1 no sugiere el desarrollo de formulaciones de brimonidina-timolol adicionando un PGA, y mucho menos bimatoprost.

Así, salta a la vista que una persona medianamente versada en la materia no habría empleado esta fuente como motivación para la búsqueda de composiciones **más eficientes, eficaces o seguras** que además incluyeran bimatoprost.

2. D2 no podría considerarse un documento que efectivamente sugiera a una persona versada en la materia a encontrar la composición reclamada, pues se basa en la combinación de dos compuestos: Brimonidina y Timolol y excipientes que normalmente se emplean en estas composiciones:

> 1. An ophthalmic pharmaceutical composition useful in the treatment of glaucoma or ocular hypertension comprising an effective amount of brimonidine and an effective amount of timolol in a pharmaceutically acceptable carrier therefor.

No se observa que D2 motive claramente al experto en la materia a incluir un componente adicional como bimatoprost a la mezcla de brimonidina+timolol+excipientes, mucho menos con el objetivo de lograr ventajas técnicas como mejorar la tolerancia y eficacia de dichas composiciones.

3. Tenemos entonces que el panorama de las enseñanzas de las anterioridades citadas por la Superintendencia era el siguiente:

   - D1 enseñaba la combinación **brimonidina-timolol** que podía estar o no administrándose de forma conjunta con las PGA's **latanoprost, bimatoprost, o travoprost.**
   - D2 enseñaba la combinación **brimonidina-timolol** y **excipientes** de uso común en tales composiciones.

Información que al ser analizada de forma objetiva no motivaría al experto en la materia ubicado en el momento previo a la fecha de prioridad (< 21-12-2009) a formular una combinación de brimonidina+timolol+bimatoprost y mucho menos teniendo una expectativa de éxito en cuanto a la seguridad y eficacia de la supuesta formulación.

El concluir que la composición de interés de mi representada era sugerida por el panorama de la información científica de D1 + D2 sólo podría realizarse si se estuviera teniendo en cuenta la información revelada por la solicitud CO 12-122-166 en el análisis de patentabilidad, es decir, si se estuviera incurriendo en un análisis en retrospectiva.

4. Con el fin de aclarar el panorama técnico previo a la fecha de prioridad de la solicitud CO-12-122-166, se presenta la publicación científica titulada: *"Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines"*, Ophthalmology, 115(7):1117-1122.e1., publicado en Febrero 20, 2008 (en adelante Stewart *et al.*)

En dicha publicación se divulga un estudio de eficacia y seguridad de principios activos para el tratamiento de la PIO:

To evaluate efficacy and safety data of currently available ocular hypotensive medicines derived from 24-hour studies, of similar design, in patients with primary open-angle glaucoma (POAG), exfoliative glaucoma, or ocular hypertension (OH).

(...)

The mean reduction of night time points was statistically lower than day time points for latanoprost (P = 0.031), timolol (P =0.032), and brimonidine (P = 0.050), but not for dorzolamide. Dorzolamide (P = 0.60), travoprost (P = 0.064), and bimatoprost (P = 0.057) did not demonstrate nighttime pressures lower than daytime ones. The mean reduction of night time points was statistically lower than that of day time points for latanoprost (P = 0.031), timolol (P = 0.032), and brimonidine (P = 0.050), but not for dorzolamide (P = 0.60), bimatoprost (P = 0.057), travoprost (P = 0.064). CONCLUSIONS: Similar relative efficacies generally exist in various classes of ocular hypotensive agents during night and day hours.

Como se observa Stewart *et al.*, no presenta datos que motiven a una persona versada en la materia a combinar tres agentes activos como se realiza en la presente solicitud.

De manera que Stewart et al., constituye una evidencia de la ausencia de guía e indicios en el arte previo a la prioridad de la solicitud CO 12-122-166 con relación a la formulación de una combinación de **bimatoprost, brimonidina y timolol.**

5. Como prueba de lo mencionado anteriormente, se desea presentar la publicación científica titulada: *"Intraocular Pressure-Lowering Effects of Commonly Used Fixed-Combination Drugs with Timolol: A Systematic Review and Meta-Analysis",* Cheng et al., PLOSone, publicada el 13 de septiembre de 2012[1]:

Esta publicación posterior a la fecha de prioridad de la solicutd CO 12-122-166 revela un estudio sobre los medicamentos más comunes que tratan la presión intraocular:

The aim of this systematic review and meta-analysis is to evaluate IOP-lowering effect of the commonly used fixed-combination drugs containing 0.5% timolol.

En este meta-análisis se revela que para maximizar la adherencia al paciente y la calidad de vida muchas combinaciones han sido desarrolladas, incluso algunas incluyendo un análogo de prostaglandina:

[1] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.00450792

More recently, to maximize patient medication adherence and quality of life, several fixed combinations of commonly used IOP-lowering medications have been developed [6]. ***Current commercially available, fixed combination drugs mostly include the topical beta-blocker 0.5% timolol combined with a prostaglandin analogue (PGA), an alpha-adrenoceptor agonist (AA) or a topical carbonic anhydrase inhibitor (CAI)*** *[7]. More and more clinical trials are published to evaluate the efficacy of these fixed-combination options. However, the non-consistent results of these studies made it difficult to draw conclusions of the degree of reduction of IOP that can be achieved with different fixed-combination drugs. Therefore, to evaluate the IOP-lowering effect of the commonly used fixed-combination drugs containing timolol, a systematic review and meta-analysis was conducted, involving all relevant published randomized clinical trials in the treatment of POAG and ocular hypertension (OHT).*

Cheng et al., (ver métodos y resultados) revela que las combinaciones con más relevancia en la práctica clínica son aquellas que contienen dos activos como brimonidina+timolol, pero no menciona que dentro de tales fármacos "*comunes*" se incluya un análogo de prostaglandina:

This 41 articles reported on 53 arms with six fixed combinations after medicine-free washout: 22 arms for ***2% dorzolamide/0.5% timolol****, 2 arms for* ***1% brinzolamide/0.5% timolol****, 5 arms for* ***0.2% brimonidine/0.5% timolol****, 14 arms for* ***0.005% latanoprost/0.5% timolol****, 8 arms for* ***0.004% travoprost/0.5% timolol****, and 2 arms for* ***0.03% bimatoprost/0.5% timolol****.*

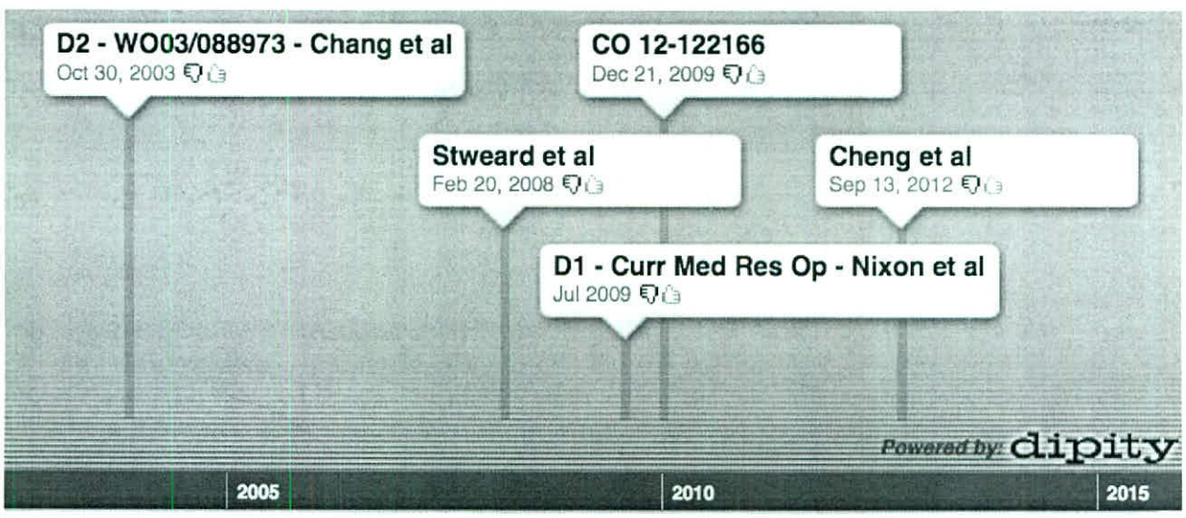
Cheng et al., además menciona que los PGA tienen un pico de acción muy diferente al del timolol por lo que no es posible determinar claramente cuál es su acción en dichas combinaciones:

The present meta-analysis found that when using as fixed combinations with timolol, dorzolamide/timolol, brinzolamide/timolol and brimonidine/timolol can result an IOP-lowering effect of more than 30%. However, the relative IOP reductions of the fixed combinations of 0.5% timolol and PGAs were only 34.8% for latanoprost/timolol, 33.0% for travoprost/timolol, and 32.9% for bimatoprost/timolol. ***One explanation is that with any fixed combination of 0.5% timolol and a PGA, a timolol dose will be omitted, leading to a lower IOP reduction [8], [51]. Because timolol has the peak effect approximately 2 hours after dosing, and prostaglandins provide maximal IOP reduction during the last half of the dosing interval (ie, post instillation hours 12 through 24) [52], the peak effect of prostaglandin-timolol fixed combinations might be provided by prostaglandins mostly, but not the combination of prostaglandins and timolol.*** *Another explanation is that the terminology concerning diurnal is not consistent in the studies reporting a mean of several IOP measurements during a (part of a) day, and only a limited number of measurements during only a part of a 24-hour period are achieved [8]. Nineteen arms from 18 trials reported a mean diurnal IOP curve of the fixed combination of timolol and a PGA. In 10 arms, all measurements were obtained within 8 hours after dosing, with three moments in 9 trials and two moments in the other one. In 6 arms, measurements were obtained in three moments up to 12 to 24 hours after installation. Full 24-hours IOP measurements were obtained in only 4 trials. If one includes only IOP measurements within a period of 8 hours or fewer after the administration of a combination of timolol and a PGA, the absence of peak efficacy moments of the PGA will lead to an underestimation of IOP-lowering effect [8].*

Entonces la información provista por Cheng et al., revela que - aun después de la fecha de prioridad de la solicitud CO 12-122-166 - las combinaciones más relevantes en la práctica clínica son las que contienen **2 agentes activos**, como **timolol+brimonidina,** y que no se consideran relevantes en el **campo técnico** las combinaciones de tres activos incluyendo PGA dados sus parámetros farmacocinéticos.

Así las cosas, la praxis clínica y los datos de parámetros farmacéuticos alejarían a una persona versada en la materia de la combinación brimonidina+timolol+bimatoprost en una misma composición. Así pues una persona situada en el panorama enfrentada al problema técnico debería vencer paradigma reinante en el momento de no incluir 3 agentes activos, para lograr la composición de la presente invención.

6. Stewart et al., y Cheng et al., han sido presentados con el fin de enriquecer el panorama de la divulgación científica del campo técnico:



Elaborado en www.dipity.com 2014

Dichos meta-análisis[2] realizados antes y después de la fecha de prioridad demuestran la carencia de indicios inequívocos acerca de las formulaciones de la combinación bimatoprost+brimonidina+timolol y sus ventajas, las cuales por el solo hecho de presentar los tres agentes activos ya sorprende al técnico medio versado en la materia.

II. LA Resolución 61404 no se considera que las enseñanzas de D1 alejen al experto de la composición de interés pues no se revelan incompatibilidades

Se considera que aunque D1 no presenta incompatibilidades, si presenta que la administración de: i) brimonidina+timolol y ii) bimatoprost, **no se realiza de forma conjunta** lo cual es evidencia para una persona medianamente versada en la materia de la existencia de características intrínsecas de cada molécula que impiden la administración conjunta de dichos fármacos.

De la revisión de otros documentos se observa que efectivamente existen diferencias en el comportamiento de los activos involucrados en esta composición y por lo tanto el experto en la materia se alejaría de tal composición.

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[2] Vale destacar que el caso del meta-análisis de Cheng et al., tiene en cuenta casi 913 documentos relacionados con el tema, veamos: "*Results : Eligiblity and Quality : The literature search identified 913 papers. Based on the content of the abstracts, 813 articles were found obviously ineligible for inclusion. From the remaining 100 articles that were retrieved for full papers, 59 had to be excluded for reasons outlined in Figure 1. Finally, 41 eligible randomized clinical trials which met our inclusion criteria were included in this systematic review [9–49].*"

Y por su parte el meta-análisis de Stewart et al., incluye 864 estudios relacionados con el tema, veamos: "*Results: This analysis included 864 separate 24-hour treatment curves from 386 patients in 28 treatment arms from 11 studies.*"

Por lo tanto, las conclusiones de estos estudios son muy importantes para comprender cual es el panorama de divulgación científica antes y después de la prioridad de la solicitud CO 12-122-166.

III. Pruebas de las ventajas técnicas sorprendentes e inesperadas de la composición reclamada

a. En cuanto a la dosificación (dosing)

En conexión con lo anterior, se pone de presente que en la técnica previa existen publicaciones que enseñan que los PGAs, como bimatoprost, son menos efectivos cuando se dosifican dos veces al día[3] .

Sin embargo, la composición de bimatoprost+brimonidina+timolol presenta efectos sorprendentes al ser dosificada dos veces al día en vez de una vez diaria[4], contrario a lo esperado de acuerdo a las enseñanzas del arte previo. A continuación se presentan tales enseñanzas:

- Linden (Drugs and Aging), página 391[5]:

La concentración óptima de latanoprost (un competidor de bimatoprost de la familia de los PGA) para reducir la PIO en pacientes humanos parece estar cerca de 50 mg/ml, es decir, 0.005%.

La reducción máxima de PIO ocurre de 6 a 12 horas después de la administración de una sola gota.

La administración una vez al día es superior a dos veces al día con relación al efecto hipotensivo ocular durante el día, es decir, la PIO permanece alta con una administración dos veces al día en comparación a una administración una vez al día.

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[3] BID
[4] QD
[5] Christina Lindén & Albert Alm *"Prostaglandin Analogues in the Treatment of Glaucoma Drugs & Aging"* Mayo de 1999; 14 (5): 387-398.

Tales resultados alejarían al técnico versado en la materia de realizar una composición de un PGA como bimatoprost o latanoprost para reducir la PIO como la de la invención, que presente ventajas en la dosificación dos veces al día.

Sin embargo, los inventores de la presente solicitud de patente encontraron que la composición de la presente invención demuestra lo contrario, lo cual apoya los resultados inesperados de la composición.

- Eisenberg (Survey of OPH) Tabla 1 (página 3)[6]:

Los datos en la Tabla 1 confirman la información existente en el momento de la presentación de la solicitud prioritaria de la presente invención, al demostrar que la persona versada en el arte esperaría que la dosificación una vez al día fuera más efectiva que la dosificación dos veces al día.

TABLE 1

Summary of IOP Results From Published Studies Comparing Bimatoprost or Travoprost to Timolol and/or Latanoprost

Study	Drug/Vehicle and Concentration	Primary Outcome	n	Duration of Treatment	Administration[a]	Baseline IOP (mm Hg)	IOP Change from Baseline (mm Hg)[b]	% IOP Change from Baseline[b]
Laibovitz[27]	bimatoprost 0.003%	change from	20	21 days qd	qd (bid)	24.9	−2.6 (−3.6 bid)	−10% (−14% bid)
	bimatoprost 0.01%	baseline	20	followed by 7	qd (bid)	25.2	−5.7* (−5.7* bid)	−22% (−22% bid)
	bimatoprost 0.03%		20	days bid	qd (bid)	27.0[f]	−7.7* (−8.2* bid)	−28% (−30% bid)
	timolol 0.5%		20		bid	25.1	−3.6	−14%
	vehicle		20		bid	24.5	−0.5	−2%
Brandt[4]	bimatoprost 0.03%	change from	234	3 months	qd	24.2	−7.7*	−32%
	bimatoprost 0.03%	baseline	243		bid	23.9	−6.4*	−27%
	timolol 0.5%		119		bid	23.8	−5.4	−22%
Sherwood[49,c]	bimatoprost 0.03%	absolute	474	6 months	qd	24.2	−7.0*	−29%
	bimatoprost 0.03%	IOP	483		bid	24.1	−6.2	−26%
	timolol 0.5%		241		bid	23.9	−5.0	−21%
DuBiner[16]	bimatoprost 0.03%	change from	21	30 days	qd	24.3[f]	−7.0	−29%
	latanoprost 0.005%	baseline	22		qd	22.9	−5.5	−24%
	vehicle		21		qd	23.4	+0.7	+0%
Gandolfi[19,d]	bimatoprost 0.03%	absolute	119	3 months	qd	24.2	−6.9	−29%
	latanoprost 0.005%	IOP	113		qd	24.0	−6.4	−26%
Goldberg[20,e]	travoprost 0.0015%	absolute	190	9 months	qd	26.5	−8.0	−30%
	travoprost 0.004%	IOP	197		qd	26.4	−8.3*	−31%
	timolol 0.5%		185		bid	26.1	−7.1	−27%
Netland[33]	travoprost 0.0015%	absolute	202	12 months	qd	25.1	−6.5*	−26%
	travoprost 0.004%	IOP	197		qd	25.5	−6.9*	−27%
	latanoprost 0.005%		193		qd	25.7	−7.0*	−27%
	timolol 0.5%		195		bid	25.7	−5.5	−21%

bid = twice daily morning and evening; IOP = intraocular pressure; qd = once daily in the evening.
[a](bid) values in parentheses are from bid phase of the study. Drug was given once daily for 21 days then twice daily for 7 days.
[b]Change and percent change are calculated from the mean of all values at the last study visit versus baseline, except for the Laibowitz study[27] which was calculated from the values at day 21 of once-daily treatment and day 7 of twice-daily treatment. The percent change values are presented for comparison purposes. Statistics were not available for all studies therefore no differences are identified.
[c]This study is a meta-analysis using pooled data from the Brandt study[4] extended to 6 months and from a previously unpublished study.
[d]Midpoint of range used because mean was not presented.
[e]Baseline data obtained by personal communication with Author and is from intent-to-treat summary.
[f]Significantly ($p < 0.05$) higher baseline IOP compared with the other groups in this study.
*Significant ($p < 0.05$) difference from timolol.

[6] Dan L. Eisenberg, MD, Carol B. Toris y Carl B. Camras, *"Bimatoprost and Travoprost: A Review of Recent Studies of Two New Glaucoma Drugs. Shepherd Eye Center"*, Survey Of Ophthalmology Volumen 47 • Suplemento 1 • Agosto de 2002

Basado en estos datos, un técnico medio versado en la materia tendría la hipótesis de que composiciones de bimatoprost son menos efectivas cuando se administra BID (dos veces diariamente por 7 días). Sin embargo, la composición de la presente invención presenta mejores resultados cuando se administra BID que cuando se administra QD (una vez al día en la mañana), de forma contraria a lo que divulgan los documentos precedentes.

Considerando todo lo anterior, siendo el objeto de los documentos D1 y D2 diferente al de la presente invención, comprendiendo materia técnica diferente, la solicitud cumple con el criterio de novedad, y teniendo en cuenta que a partir de la lectura de D1 y D2 un técnico medio en la materia no podría derivar de forma obvia la materia de la invención denegada, además porque tendría que superar el prejuicio existente en el momento, y además demostrar los resultados ventajosos sobre la efectividad, seguridad y forma de dosificación para la composición reivindicada, la invención denegada no es obvia, cumpliendo así con el requisito inventivo.

a. En cuanto a la Eficacia y Seguridad

Con el fin de demostrar la superioridad de las composiciones reclamadas se presenta un estudio clínico en el cual se evaluó la eficacia y seguridad de:

i) una solución oftálmica conteniendo 0,01% Bimatoprost/0,15% brimonidina tartrato/ 0,5 % timolol (en adelante COMBINACIÓN TRIPLE)

ii) una solución oftálmica conteniendo 0,15% brimonidina tartrato/ 0,5 % timolol (en adelante COMBIGAN)

Encontrándose que la COMBINACION TRIPLE presenta un efecto técnico superior sobre COMBIGAN pues logró corregir la PIO de los pacientes incluidos con mayor eficacia:

Efficacy:

- The primary efficacy analyses demonstrated the statistical superiority of TRIPLE COMBINATION over COMBIGAN. At week 12, TRIPLE COMBINATION provided -0.85 mm Hg ($p = 0.028$) greater mean IOP change from baseline compared to COMBIGAN in the mITT population.
- Statistical superiority of TRIPLE COMBINATION over COMBIGAN was also observed at all other study visits. At weeks 1, 2, 4, and 8, TRIPLE COMBINATION provided greater mean IOP change from baseline compared to COMBIGAN (week 1: -1.28 mm Hg [$p = 0.006$]; week 2: -1.40 mm Hg [$p = 0.001$]; week 4: -0.92 mm Hg [$p = 0.019$]; week 8: -0.85 mm Hg [$p = 0.047$]) in the mITT population.

Así mismo, el estudio demostró que la COMBINACION TRIPLE presenta mayor seguridad que COMBIGAN:

Safety:

- The vast majority of adverse events were ocular in nature. Of these, only conjunctival hyperaemia, eye irritation, and dry eye were statistically significantly greater in the TRIPLE COMBINATION group than the COMBIGAN group ($p \leq 0.016$). These were also the most frequently reported treatment-related adverse events and were mostly reported as mild in severity. These adverse events resulted in only 5 discontinued patients (conjunctival hyperaemia [3/93 (3.2%)] and eye irritation [2/93 (2.2%)]) in the TRIPLE COMBINATION group.
- Four serious adverse events were reported in 3 patients (3/191 [1.6%]). None were ocular. All 3 patients with serious adverse events were in the TRIPLE COMBINATION group. None of these serious adverse events were considered treatment-related, and there were no deaths reported during the study period.

En conclusión, la COMBINACION TRIPLE disminuye la PIO de forma más eficiente y segura que COMBIGAN:

Conclusion:

TRIPLE COMBINATION provides a clinically meaningful and statistically significantly greater IOP-lowering effect than COMBIGAN, and has an acceptable safety and tolerability profile in patients with primary open-angle glaucoma or ocular hypertension with elevated IOP.

Para la consideración de que Despacho adjunto los siguiente documentos antes aludidos, que evidencian la actividad ventajosa sobre las composiciones conocidas para tratar el glaucoma, que comprenden solamente brimonidina y timolol.

- Stewart et al., *"Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines"*, Ophthalmology, 115(7):1117-1122.e1., publicado en Febrero 20, 2008

- Cheng et al., *"Intraocular Pressure-Lowering Effects of Commonly Used Fixed-Combination Drugs with Timolol: A Systematic Review and Meta-Analysis"*, PLOSone, publicada el 13 de septiembre de 2012

- Christina Lindén & Albert Alm *"Prostaglandin Analogues in the Treatment of Glaucoma Drugs & Aging"* Mayo de 1999; 14 (5): 387-398.

- Dan L. Eisenberg, MD, Carol B. Toris y Carl B. Camras, *"Bimatoprost and Travoprost: A Review of Recent Studies of Two New Glaucoma Drugs. Shepherd Eye Center"*, Survey Of Ophthalmology Volumen 47 • Suplemento 1 • Agosto de 2002

- Clinical Studio Report: "A Multicenter, Double-masked, Randomized Study to Evaluate the Safety and Efficacy of Twice-daily 0.01% Bimatoprost / 0.15% Brimonidine Tartrate / 0.5% Timolol Ophthalmic Solution (Triple Combination) Compared With Twice-daily COMBIGAN® in Patients Who Have Primary Open-angle Glaucoma or Ocular Hypertension"

Los anteriores argumentos y los documentos adjuntos son aplicables a los argumentos de las oposiciones presentadas a esta solicitud.

Por lo expuesto, ratifico mi petición de que se reponga la Resolución recurrida, para que en su lugar se ordene la expedición del privilegio de invención propuesto.

Del señor Superintendente,

JERÓNIMO CASTILLO BONILLA
C.C. 79.462.057 Bogotá
T.P 104167 C.S. Judicatura

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PubMed

Abstract

ELSEVIER FULL-TEXT ARTICLE

Ophthalmology. 2008 Jul;115(7):1117-1122.e1. Epub 2008 Feb 20.

Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines.

Stewart WC[1], Konstas AG, Nelson LA, Kruft B.

Author information

Abstract

PURPOSE: To evaluate efficacy and safety data of currently available ocular hypotensive medicines derived from 24-hour studies, of similar design, in patients with primary open-angle glaucoma (POAG), exfoliative glaucoma, or ocular hypertension (OH).

DESIGN: Meta-analysis of published articles evaluating patients with POAG, exfoliative glaucoma, or OH.

METHODS: We included articles that were randomized, prospective, single- or double-masked, comparative studies of ocular hypotensive therapies over 24 hours. Each article selected contained an untreated baseline, >or=4-week treatment period, >/=20 patients per treatment arm, and >or=6 time points not spaced >5 hours apart and used Goldmann applanation or Tonopen tonometry (supine measurements) to measure intraocular pressure (IOP).

MAIN OUTCOME MEASURE: Twenty-four-hour IOP efficacy.

RESULTS: This analysis included 864 separate 24-hour treatment curves from 386 patients in 28 treatment arms from 11 studies. A statistical difference in the mean diurnal pressure decrease existed between monotherapy treatments for POAG/OH patients, with bimatoprost (29%) and travoprost (27%) showing the greatest 24-hour reduction (P = 0.026). Timolol 0.5% was less effective than latanoprost (24% vs. 19% reduction) but decreased the pressure at each night time point (P = 0.0003). Dorzolamide showed a 19% 24-hour pressure reduction and brimonidine 0.2% a 14% one. In exfoliative glaucoma patients, latanoprost and travoprost showed higher baseline and treatment pressures, although the pressure reductions (29% and 31%, respectively) were greater generally than observed with POAG/OH. An evening-dosed latanoprost/timolol fixed combination reduced the pressure 33%, and the dorzolamide/timolol fixed combination (DTFC), 26%. However, the power to detect a difference for this specific comparison was probably low, due to the limited number of patients (n = 20) in the DTFC group. A statistical difference between evening-dosed (24%) and morning-dosed (18%) latanoprost (P<0.0001) was noted, but not between evening (27%) and morning (26%) travoprost (P = 0.074). The mean reduction of night time points was statistically lower than day time points for latanoprost (P = 0.031), timolol (P =

0.032), and brimonidine (P = 0.050), but not for dorzolamide. Dorzolamide (P = 0.60), travoprost (P = 0.064), and bimatoprost (P = 0.057) did not demonstrate nighttime pressures lower than daytime ones. The mean reduction of night time points was statistically lower than that of day time points for latanoprost (P = 0.031), timolol (P = 0.032), and brimonidine (P = 0.050), but not for dorzolamide (P = 0.60), bimatoprost (P = 0.057), travoprost (P = 0.064).

CONCLUSIONS: Similar relative efficacies generally exist in various classes of ocular hypotensive agents during night and day hours.

Comment in

Relative efficacy of prostaglandins. [Ophthalmology. 2009]
Corneal thickness and glaucoma medications. [Ophthalmology. 2009]

PMID: 18082886 [PubMed - indexed for MEDLINE]

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Intraocular Pressure-Lowering Effects of Commonly Used Fixed-Combination Drugs with Timolol: A Systematic Review and Meta-Analysis

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Abstract

Background: The first goal of medical therapy in glaucoma is to reduce intraocular pressure (IOP), and the fixed-combination medications are needed to achieve sufficiently low target IOP. The aim of this systematic review and meta-analysis is to evaluate IOP-lowering effect of the commonly used fixed-combination drugs containing 0.5% timolol.

Methods: Pertinent publications were identified through systematic searches. Over 85% of the patients had to be diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). Forty-one randomized clinical trials were included in the meta-analysis. The main efficacy measures were the absolute and relative values of mean diurnal IOP reduction, and the highest and lowest IOP reductions on the diurnal IOP curve. The pooled 1- to 3-month IOP-lowering effects after a medicine-free washout period was calculated by performing meta-analysis using the random effects model, and relative treatment effects among different fixed combinations were assessed using a mixed-effects meta-regression model.

Results: The relative reductions for mean diurnal IOP were 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. For the highest IOP decrease, relative reductions ranged from 31.3% for dorzolamide/timolol to 35.5% for travoprost/timolol; for the lowest IOP decrease, those varied from 25.9% for dorzolamide/timolol to 33.1% for bimatoprost/timolol. Both latanoprost/timolol and travoprost/timolol were more effective in lowering mean diurnal IOP than brimonidine/timolol (WMD: 5.9 and 7.0) and dorzolamide/timolol (WMD: 3.8 and 3.3).

Conclusions: All six commonly used fixed-combination drugs containing timolol can effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travoprost/timolol might achieve better IOP-lowering effects among the six fixed-combination agents.

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Introduction

Glaucoma has been established as the second leading cause of world blindness, which may affect 60.5 million people worldwide in 2010, and 79.6 million in 2020, and approximately 74% of glaucoma patients have primary open-angle glaucoma (POAG) [1]. The treatment of glaucoma focuses mainly on lowering intraocular pressure (IOP) [2]. The target IOP is often set to a level 20% to 30% of IOP reduction, and consequent large IOP reduction beyond 30% or even 40% in cases of advanced glaucoma.

In the last two decades, several novel classes of topical IOP-lowering drugs have been available, and now there are more choices in the treatment of glaucoma. A recent meta-analysis of the IOP-lowering effect of glaucoma drugs showed a maximum mean IOP reduction of 33% from baseline IOP in the case of monotherapy [3]. However, many patients require more than one medication to achieve adequate IOP reduction [4,5].

More recently, to maximize patient medication adherence and quality of life, several fixed combinations of commonly used IOP-lowering medications have been developed [6]. Current commercially available, fixed combination drugs mostly include the topical beta-blocker 0.5% timolol combined with a prostaglandin analogue (PGA), an alpha-adrenoceptor agonist (AA) or a topical carbonic anhydrase inhibitor (CAI) [7]. More and more clinical trials are published to evaluate the efficacy of these fixed-combination options. However, the non-consistent results of these studies made it difficult to draw conclusions of the degree of

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reduction of IOP that can be achieved with different fixed-combination drugs. Therefore, to evaluate the IOP-lowering effect of the commonly used fixed-combination drugs containing timolol, a systematic review and meta-analysis was conducted, involving all relevant published randomized clinical trials in the treatment of POAG and ocular hypertension (OHT).

Methods

Outcome Measures

The outcome measures of efficacy were the absolute and relative IOP reductions from baseline. The standard time point of measurement was 1 month or the closest time point, with minimally 1 month and maximally 3 months. The mean diurnal IOP curve, the highest IOP decrease on the diurnal IOP curve, and the lowest IOP decrease on the diurnal IOP curve were noted [8].

Search Strategy and Trials Selection

Randomized clinical trials were identified through a systematic search of PubMed, Embase, and the Cochrane Controlled Trials Register. The keywords for the medication were *timolol, dorzolamide, brinzolamide, brimonidine, latanoprost, travoprost,* and *bimatoprost.* The keywords for the disease were *glaucoma,* and *ocular hypertension.* The limit for the search was *randomized controlled trial.* The computerized searches covered the period between January 1, 1998, and September 1, 2011. Additional studies were also identified by a hand search of all the references of retrieved articles. The internet was searched using the Google™ and Yahoo!® search engines to obtain information.

Published clinical trials were selected based on the protocol-determined selection criteria. (i) Study design: randomized clinical trials, including parallel or crossover design. (ii) Population: over 85% of the patients had to be diagnosed with POAG or OHT. (iii) Intervention: after a medicine-free washout period, at least one of the following fixed-combination drugs, including 2% dorzolamide/0.5% timolol twice daily, 1% brinzolamide/0.5% timolol twice daily, 0.2% brimonidine/0.5% timolol twice daily, 0.005% latanoprost/0.5% timolol once daily, 0.004% travoprost/0.5% timolol once daily, and 0.03% bimatoprost/0.5% timolol once daily. (iv) Outcome variables: absolute and relative reductions from baseline in IOP. (v) Duration: at least one of time point between 1 month and 3 months.

Two reviewers (JWC, SWC) determined the trial eligibility independently. Firstly, the titles and abstracts of the obtained publications were screened. Then, full articles of the remaining identified publications were scrutinized. Only trials meeting selection criteria were assessed for methodological quality.

Data Extraction and Qualitative Assessment

Data extraction was performed according to the customized protocol by two reviewers (JWC, SWC) independently. Any disagreement was resolved by discussion. A customized form for data extraction was used as follows. (i) Publications: the first author and published year. (ii) Method: duration, randomization technique, allocation concealment method, group design (parallel, crossover), masking (participants, investigators, examiners), country, and setting. (iii) Participants: inclusion criteria, exclusion criteria, sampling, disease types, age, sex, and withdrawals/losses to follow up (reason). (iv) Interventions: interventions (drugs, dose, route, duration), and co-medications (drugs, dose, route, duration). (v) Outcomes: definitions, measuring method, measuring time, time points, results. (vi) Statistics: simple size determination, intention-to-treat analysis, and per-protocol analysis.

Eligible studies that met inclusion criteria were rated for methodological quality by two authors independently, using a guide developed from the Delphi list for quality assessment of randomized clinical trials [3]. Each item in this quality list had the same weight. For each publication, a quality score was calculated, where "yes" was scored as 1 point for a certain quality item and "no" and "do not know" were scored as 0 point. The quality of sample studies scored out of a maximum of 18 (**Table 1**).

Statistical Analysis

All statistical analyses were performed using Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood Cliffs, New Jersey) (http://www.meta-analysis.com). Outcome measure was assessed on an intention-to-treat (ITT) basis. For each study, absolute and relative IOP reductions and 95% confidence intervals (CIs) of the fixed-combination drugs were calculated. We first obtained the pooled estimates of IOP reductions with 95% CIs by fixed-combination medication using the random-effects model. Then, a mixed-effects meta-regression model was used to estimate the weighted mean differences (WMDs) in relative IOP reductions by different fixed combinations. Egger's weighted regression method was used to statistically assess publication bias.

Results

Eligiblity and Quality

The literature search identified 913 papers. Based on the content of the abstracts, 813 articles were found obviously ineligible for inclusion. From the remaining 100 articles that were retrieved for full papers, 59 had to be excluded for reasons outlined in **Figure 1**. Finally, 41 eligible randomized clinical trials which met our inclusion criteria were included in this systematic review [9–49].

This 41 articles reported on 53 arms with six fixed combinations after medicine-free washout: 22 arms for 2% dorzolamide/0.5% timolol, 2 arms for 1% brinzolamide/0.5% timolol, 5 arms for 0.2% brimonidine/0.5% timolol, 14 arms for 0.005% latanoprost/0.5% timolol, 8 arms for 0.004% travoprost/0.5% timolol, and 2 arms for 0.03% bimatoprost/0.5% timolol.

The mean total quality score for all studies was 16.2 with a range from 13 to 18 (**Table 2**). Twelve studies were scored less than 16, and 29 trials were scored 16 and more. There were only seven items sometimes scored as 0 point (**Table 1**), including allocation concealment, blinding, intention-to-treat analysis, withdrawals, and sample size.

The *P* values of Egger's measure of publication bias were 0.25 for mean diurnal IOP reduction, 0.13 for the highest IOP reduction, and 0.51 for the lowest IOP reduction. Because no relevant differences were observed by statistics, no publication bias was found.

Design and Characteristics

The study design and baseline characteristics of the eligible studies are summarized in **Table 2**. Randomized clinical trials were undertaken in Europe, U.S., Canada, Latin America, Australia, Israel, Turkey, Singapore, and Taiwan. Twenty-seven trials had a prospective, parallel design, and fourteen had a prospective, crossover design. The proportion of withdrawals varied from 0.0% to 25.7%.

Overall, 5261 patients were involved, with the mean age was 63.5 years (range from 56.1 to 68.0 years). The proportion of patients with POAG or OHT per study varied from 91% to 100%. The mean baseline IOP ranged from 22.0 mmHg to 30.2 mmHg after a medicine-free washout period.

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Table 1. Quality items of the quality assessment system of methodological characteristics.*

Item code	Quality item	No. of trials scored "Yes"
A	Was a method of randomization used?	41
B	Was the treatment allocation concealed?	22
C	Were the participants blinded?	22
D	Were the investigators blinded?	33
E	Were the examiners blinded?	39
F	Were inclusion criteria specified?	41
G	Were exclusion criteria specified?	41
H	Were the interventions described explicitly?	41
I	Was comedication avoided or standardized?	41
J	Were point estimates and measures of variability presented for the primary outcome measures?	41
K	Was the period of outcome measurements equal for all groups?	41
L	Were times of IOP measurements equal for all-groups?	41
M	Was information about the method of IOP measurement presented?	41
N	Were the groups similar at baseline regarding the most important prognostic indicators?	41
O	Was it unlikely that compliance may explain differences between groups?	41
P	Was withdrawal rate reported	39
Q	Was calculation of sample size reported	33
R	Was an intention-to-treat analysis performed?	27

IOP = intraocular pressure.
*The system was developed from the Delphi list, and was supplemented with additional items which were important for interpreting IOP measurements.
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Intraocular Pressure Lowering Effects

Forty-four arms were reporting the mean diurnal IOP reduction; 46 arms were reporting the highest IOP reduction; and 38 arms were reporting the lowest IOP reduction. **Table 3** gives an overview of the absolute and relative values of mean diurnal IOP reduction, and the highest and lowest IOP decrease on the diurnal IOP curve.

The pooled absolute reductions in mean diurnal IOP curve were 7.41 mmHg (95% CI, 6.69 to 8.12) for dorzolamide/timolol, 8.33 mmHg (6.82 to 9.84) for brinzolamide/timolol, 6.55 mmHg (5.59 to 7.40) for brimonidine/timolol, 8.85 mmHg (8.30 to 9.40) for latanoprost/timolol, 9.09 mmHg (8.32 to 9.87) for travoprost/timolol, and 8.40 mmHg (8.13 to 8.67) for bimatoprost/timolol (**Table 4**). The relative mean diurnal IOP reductions were 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. Both latanoprost/timolol and travoprost/timolol were found to produce greater IOP-lowering effects than dorzolamide/timolol and brimonidine/timolol (**Table 5**).

The absolute values of the highest IOP reductions varied from 7.59 mmHg for brimonidine/timolol to 9.49 mmHg for travoprost/timolol, and the relative reductions ranged from 31.3% for dorzolamide/timolol to 35.5% for travoprost/timolol (**Table 4**). Travoprost/timolol and bimatoprost/timolol produced greater relative reductions than dorzolamide/timolol,

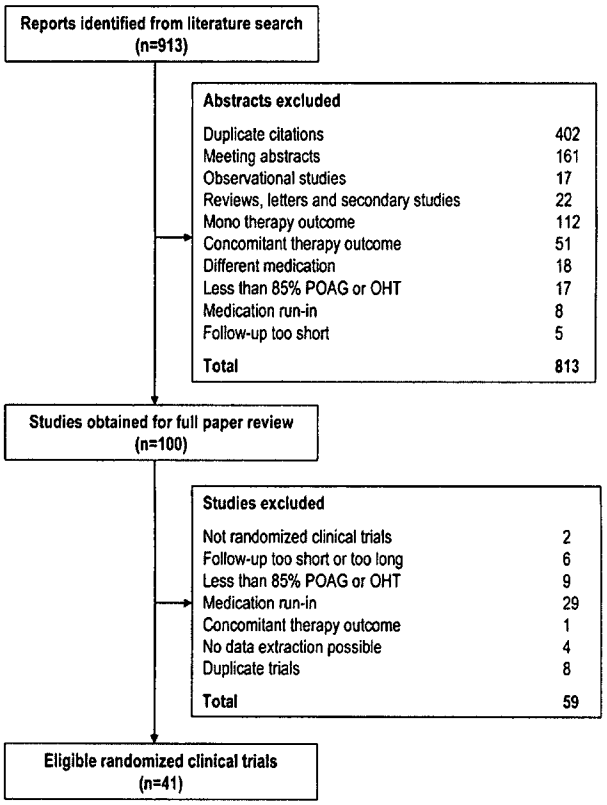

Figure 1. The selection flowchart of the studies included in the present meta-analysis.
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with WMDs being 4.2 (0.6 to 7.8), 3.6 (2.3 to 5.0) respectively (Table 5).

The pooled results of absolute and relative values of the lowest IOP reductions of six fixed combinations are also shown in **Table 4**. Travoprost/timolol was significantly more effective in lowering IOP than dorzolamide/timolol (WMD: 6.7; 95% CI, 1.5 to 12.0), and brimonidine/timolol (WMD: 6.6; 95% CI, 1.9 to 11.4); and latanoprost/timolol also was significantly more effective than dorzolamide/timolol (WMD: 6.2; 95% CI, 1.4 to 10.9) and brimonidine/timolol (WMD: 6.0; 95% CI, 0.9 to 11.1) (**Table 5**).

Discussion

This systematic review and meta-analysis of data from 40 randomized clinical trials reveal that all six commonly used fixed-combination drugs containing 0.5% timolol can effectively lower IOP in patients with POAG and OHT. After completely washing out all medication, the mean diurnal IOP reductions ranged from 6.55 mmHg for brimonidine/timolol to 9.09 mmHg for travoprost/timolol; the highest IOP reductions varied from 7.59 mmHg for brimonidine/timolol to 9.49 mmHg for travoprost/timolol; and the lowest IOP reductions ranged from 5.87 mmHg for brimonidine/timolol to 7.99 mmHg for travoprost/timolol.

The overview of relative IOP reductions at diurnal curve showed that travoprost/timolol, bimatoprost/timolol, and latanoprost/timolol were the three most effective fixed-combinations. The mixed-effects meta-regression results revealed that latanoprost/timolol and travoprost/timolol were more effective than dorzolamide/timolol and brimonidine/timolol. However, the difference for bimatoprost/timolol was not statistically significant,

Table 2. Baseline characteristics of eligible randomized clinical trials.

Trial	Design	Location	Centre	Intervention			Total no.	Withdrawals (%)	Mean age (years)	Sex (M/F)	POAG or OHT (%)	Baseline IOP* (mm Hg) [mean (SD)]	Quality score
				Medication	Route	Duration							
199810/01 [9]	DB, PG	U.S.	27	2.0% Dorzolamide/ 0.5% timolol	8:30 AM, 8:30 PM	3 Months	114	0.3	62.4	54/60	100	27.8 (5.0)	18
200303/01 [10]	DB, PG	U.S.	8	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	3 Months	29	0.0	62.7	9/20	97	25.4 (3.7)	14
200304/01 [11]	DB, CR	Italy	1	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	1 Month	20	0.0	63.0	9/11	100	24.9 (0.9)	17
200307/01 [12]	SB, CR	Greece	2	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	6 Weeks	33	2.9	64.8	15/18	100	25.8 (1.4)	14
200402/01 [13]	DB, PG	U.S., Europe, Israel	44	2.0% Dorzolamide/ 0.5% timolol	8 AM, 10 PM	3 Months	273	8.8	62.8	125/148	99	-	18
200402/02 [14]	SB, PG	U.S.	30	0.005% Latanoprost/ 0.5% timolol 2.0% Dorzolamide/ 0.5% timolol	8 AM 8 AM, 8 PM	3 Months	251	4.3	63.5	112/139	98	28.4 (3.7)	16
200405/01 [15]	OL, PG	Latin America	13	2.0% Dorzolamide/0.5% timolol	8 AM, 8 PM	8 Weeks	117	6.0	61.1	47/70	92	25.0 (3.6)	15
200407/01 [16]	SB, PG	Europe	34	0.005% Latanoprost/ 0.5% timolol	8 AM	6 Months	163	6.0	65.5	73/90	96	27.4 (2.6)	17
200409/01 [17]	SB, PG	Spain	1	0.005% Latanoprost/ 0.5% timolol	9 AM	3 Months	22	0.0	63.5	9/13	100	24.7 (2.5)	13
200410/01 [18]	DB, CR	U.S.	3	0.005% Latanoprost/ 0.5% timolol	8 AM	6 Weeks	35	8.6	64.5	12/23	97	26.9 (3.2)	16
200505/01 [19]	DB, CR	U.S.	3	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	8 Weeks	32	8.6	61.5	9/23	100	25.9 (2.4)	16
200507/01 [20]	DB, PG	U.S.	33	0.004% Travoprost/ 0.5% timolol	8 AM	3 Months	82	3.9	63.0	37/45	100	30.2 (2.7)	18
200507/02 [21]	SB, CR	Greece	1	0.005% Latanoprost/ 0.5% timolol	8 PM	8 Weeks	37	0.0	65.8	14/23	100	26.5 (2.8)	17
200508/01 [22]	DB, PG	U.S.	27	0.004% Travoprost/ 0.5% timolol	8 AM	3 Months	155	7.7	62.0	63/92	97	25.6 (2.7)	18
200510/01 [23]	DB, PG	U.S.	19	0.004% Travoprost/ 0.5% timolol	8 AM	3 Months	151	7.5	64.2	57/94	97	25.3 (2.3)	18
200601/01 [24]	DB, PG	Europe, Canada	53	0.005% Latanoprost/ 0.5% timolol	8 PM	12 Weeks	255	11.0	65.0	129/126	91	26.0 (2.3)	18
200603/01 [25]	DB, PG	France	Multi	0.004% Travoprost/ 0.5% timolol 0.004% Travoprost/0.5% timolol	9 AM 9 PM	6 Weeks	91	8.8	63.9	46/45	90	26.7 (3.3)	18
200603/02 [26]	SB, PG	Brazil	1	0.005% Latanoprost/ 0.5% timolol	7 AM	1 Month	14	0.0	59.2	-	100	22.0 (3.2)	13
200609/01 [27]	DB, PG	U.S.	53	0.2% Brimonidine/0.5% timolol	8 AM, 8 PM	12 Months	385	25.7	62.0	181/204	100	24.7 (2.7)	18

Table 2. Cont.

Trial	Design	Location	Centre	Intervention			Total no.	Withdrawals (%)	Mean age (years)	Sex (M/F)	POAG or OHT (%)	Baseline IOP* (mm Hg) [mean (SD)]	Quality score
				Medication	Route	Duration							
200609/02 [28]	SB, PG	Brazil	1	2.0% Dorzolamide/ 0.5% timolol	9 AM, 9 PM	6 Weeks	27	0.0	57.5	8/19	100	23.1 (2.1)	14
200611/01 [29]	SB, CR	Greece	1	0.005% Latanoprost/ 0.5% timolol	8 PM	8 Weeks	34	2.9	62.4	13/21	100	27.2 (2.9)	15
200702/01 [30]	SB, CR	Turkey	1	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	6 Months	29	3.3	64.9	15/14	100	24.0 (2.2)	13
200704/01 [31]	SB, CR	Brazil	1	0.2% Brimonidine/ 0.5% timolol 2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	4 Weeks	30	0.0	56.1	12/18	100	22.9 (1.6)	16
200801/01 [32]	SB, CR	Greece	2	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	6 Months	53	8.6	61.2	21/32	100	27.1 (2.6)	15
200804/01 [33]	DB, PG	U.S., Canada	59	0.03% Bimatoprost/ 0.5% timolol	8 AM	3 Months	533	6.6	62.1	247/286	100	25.9 (3.1)	18
200808/01 [34]	DB, CR	U.S.	2	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	8 Weeks	29	3.3	68.0	11/18	100	25.1 (2.0)	16
200808/02 [35]	DB, PG	U.S.	19	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	8 Weeks	117	6.0	61.8	47/70	99	26.2 (3.4)	18
200810/01 [36]	SB, CR	Greece	1	2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	6 Weeks	27	0.0	61.0	11/16	100	26.4 (1.6)	16
200810/02 [37]	DB, PG	U.S.	35	1.0% Brinzolamide/ 0.5% timolol	8 AM, 8 PM	6 Months	171	7.5	-	80/91	95	27.2 (2.7)	16
200811/01 [38]	SB, CR	Greece	2	0.2% Brimonidine/ 0.5% timolol	8 AM, 8 PM	3 Months	28	12.5	63.6	18/10	100	26.9 (2.8)	16
200812/01 [39]	OL, PG	Brazil, Argentina	5	0.2% Brimonidine/ 0.5% timolol 2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	8 Weeks	210	7.6	60.4	87/123	100	24.0 (4.0)	14
200904/01 [40]	DB, CR	Greece	1	0.004% Travoprost/ 0.5% timolol	10 PM	8 Weeks	34	5.9	63.9	15/19	100	28.9 (3.3)	17
200904/02 [41]	DB, PG	U.S., Europe, Australia, Singapore, Taiwan	Multi	1.0% Brinzolamide/ 0.5% timolol 2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	12 Months	437	10.1	64.8	181/256	91	27.3 (6.9)	18
200905/01 [42]	DB, CR	Greece	1	0.005% Latanoprost/ 0.5% timolol	8 PM	8 Weeks	29	3.3	63.7	13/16	100	27.7 (1.9)	16
200907/01 [43]	SB, PG	U.S.	10	0.2% Brimonidine/0.5% timolol 2.0% Dorzolamide/ 0.5% timolol	8 AM, 8 PM	3 Months	180	10.6	67.7	80/100	100	23.3 (4.6)	16
200910/01 [44]	OL, PG	Brazil	1	0.005% Latanoprost/ 0.5% timolol	8 PM	8 Weeks	18	0.0	57.8	8/10	100	24.7 (1.3)	14

Table 2. Cont.

Trial	Design	Location	Centre	Intervention			Total no.	Withdrawals (%)	Mean age (years)	Sex (M/F)	POAG or OHT (%)	Baseline IOP* (mm Hg) [mean (SD)]	Quality score
				Medication	Route	Duration							
200911/01 [45]	DB, PG	Europe, Turkey	31	0.004% Travoprost/ 0.5% timolol 2.0% Dorzolamide/ 0.5% timolol	9 AM 9 PM	AM, 96 Weeks	319	2.8	61.7	122/197	92	27.0 (3.4)	17
201002/01 [46]	DB, PG	U.S.	Multi	0.005% Latanoprost/ 0.5% timolol	8 PM	12 Weeks	129	11.6	64.8	57/72	98	29.0 (3.0)	18
201007/01 [47]	SB, PG	Europe	25	0.005% Latanoprost/ 0.5% timolol 2.0% Dorzolamide/0.5% timolol	8 PM 8 AM, 8 PM	12 Weeks	270	4.8	66.2	121/149	91	27.3 (3.7)	17
201007/02 [48]	DB, PG	U.S., Canada	45	0.005% Latanoprost/ 0.5% timolol	8 PM	12 Weeks	170	11.8	65.3	76/94	96	28.7 (2.6)	18
201102/01 [49]	SB, PG	Spain	1	0.005% Latanoprost/ 0.5% timolol 0.004% Travoprost/0.5% timolol 0.03% Bimatoprost/0.5% timolol	9 PM	12 Months	128	9.2	68.0	41/87	100	27.3 (4.0)	15

M = male; F = female; IOP = intraocular pressure; SD = standard deviation.
DB = double blind; SB = single blind; OL = open label; PG = parallel group; CR = crossover.
*Pooled values, measurements closest to 8 AM.
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Table 3. Absolute and relative reductions in IOP for mean diurnal curve, the highest and lowest IOP decrease per study arm.

Trial	Medication	End point of measurement (weeks)	Type of measurement	Time points (hours after dosing)	Highest (SE)		Lowest (SE)		Diurnal (SE)	
					Absolute (mm Hg)	Relative (%)	Absolute (mm Hg)	Relative (%)	Absolute (mm Hg)	Relative (%)
199810/01 [9]	2.0% Dorzolamide/0.5% timolol	4	IOP Curve (2)	0, 2	9.30 (0.41)	33.70 (1.23)	8.00 (0.42)	28.20 (1.22)	8.65 (0.42)	30.95 (1.23)
200303/01 [10]	2.0% Dorzolamide/0.5% timolol	4	Single (1)	2	6.70 (0.82)	26.17 (3.22)	-	-	-	-
	2.0% Dorzolamide/0.5% timolol	6	Single (1)	2	6.30 (0.54)	25.10 (2.16)	-	-	-	-
200304/01 [11]	2.0% Dorzolamide/0.5% timolol	4	IOP Curve (8)	0, 3, 6, 9	9.50 (0.18)	38.17 (0.74)	3.90 (0.25)	18.19 (1.18)	6.10 (0.49)	26.99 (2.17)
200307/01 [12]	2.0% Dorzolamide/0.5% timolol	6	IOP Curve (6)	2, 6, 10	-	-	-	-	10.50 (0.31)	40.70 (1.20)
200402/01 [13]	2.0% Dorzolamide/0.5% timolol	4	IOP Curve (4)	0, 2, 6, 8	-	-	-	-	6.80 (0.36)	-
	2.0% Dorzolamide/0.5% timolol	4	IOP Curve (4)	0, 2, 6, 8	-	-	-	-	7.49 (0.30)	-
200402/02 [14]	0.005% Latanoprost/0.5% timolol	13	IOP Curve (3)	0, 4, 8	9.60 (0.39)	33.33 (1.37)	9.10 (0.32)	32.97 (1.17)	9.40 (0.28)	33.69 (0.99)
	2.0% Dorzolamide/0.5% timolol	13	IOP Curve (3)	0, 4, 8	8.90 (0.39)	32.36 (1.41)	8.10 (0.39)	29.03 (1.39)	8.40 (0.33)	30.55 (1.19)
200405/01 [15]	2.0% Dorzolamide/0.5% timolol	8	IOP Curve (4)	0, 2, 6, 9	7.40 (0.32)	29.60 (1.29)	5.40 (0.39)	23.89 (1.72)	6.40 (0.30)	27.12 (1.25)
200407/01 [16]	0.005% Latanoprost/0.5% timolol	4	IOP Curve (3)	0, 4, 8	-	-	-	-	9.11 (0.18)	34.51 (0.67)
200409/01 [17]	0.005% Latanoprost/0.5% timolol	4	IOP Curve (3)	0, 3, 7	6.40 (0.59)	26.12 (2.40)	6.20(0.46)	25.41 (1.88)	6.29 (0.43)	25.59 (1.75)
200410/01 [18]	0.005% Latanoprost/0.5% timolol	6	IOP Curve (3)	0, 4, 8	8.30(0.68)	30.86 (2.51)	8.00 (0.65)	30.88 (2.53)	8.20(0.51)	31.54 (1.97)
200505/01 [19]	2.0% Dorzolamide/0.5% timolol	8	IOP Curve (3)	0, 2, 8	7.30(0.64)	29.44 (2.58)	6.10 (0.57)	25.42 (2.36)	6.80(0.46)	27.31 (1.85)
200507/01 [20]	0.004% Travoprost/0.5% timolol	6	IOP Curve (3)	0, 2, 8	11.30 (0.46)	37.42 (1.52)	9.20 (0.42)	33.82 (1.54)	10.43 (0.44)	36.38 (1.53)
200507/02 [21]	0.005% Latanoprost/0.5% timolol	8	IOP Curve (6)	3, 6, 10, 14, 18, 22	10.10 (0.39)	38.11 (1.47)	6.10 (0.41)	26.87 (1.81)	7.50 (0.28)	30.99 (1.16)
200508/01 [22]	0.004% Travoprost/0.5% timolol	6	IOP Curve (3)	0, 2, 8	8.60 (0.22)	33.20 (0.86)	6.90 (0.26)	29.20 (1.13)	7.63 (0.24)	30.97 (0.99)
200510/01 [23]	0.004% Travoprost/0.5% timolol	6	IOP Curve (3)	0, 2, 8	9.40 (0.22)	37.15 (0.85)	7.40 (0.21)	32.17 (0.92)	8.37 (0.22)	34.63 (0.88)
200601/01 [24]	0.005% Latanoprost/0.5% timolol	12	IOP Curve (3)	12, 16, 20	9.10 (0.20)	35.00 (0.77)	8.20 (0.20)	33.20 (0.81)	8.70 (0.20)	34.25 (0.79)
200603/01 [25]	0.004% Travoprost/0.5% timolol	6	IOP Curve (3)	0, 2, 7	10.10 (0.68)	37.80 (2.74)	8.34 (0.63)	33.90 (2.36)	9.26 (0.68)	35.90 (2.63)
	0.004% Travoprost/0.5% timolol	6	IOP Curve (3)	12, 14, 19	9.60 (0.68)	36.10 (2.73)	8.70 (0.63)	34.40 (2.37)	9.20 (0.68)	35.20 (2.63)
200603/02 [26]	0.005% Latanoprost/0.5% timolol	4	Single (1)	3	-	-	8.50 (0.94)	38.60 (2.33)	-	-
200609/01 [27]	0.2% Brimonidine/0.5% timolol	6	IOP Curve (4)	0, 2, 7, 9	7.49 (0.17)	32.15 (0.73)	4.98 (0.20)	22.84 (0.92)	6.17 (0.19)	26.85 (0.83)
200609/02 [28]	2.0% Dorzolamide/0.5% timolol	6	IOP Curve (4)	3, 7, 11	6.20 (0.37)	26.84 (1.58)	2.90 (0.52)	15.59 (2.79)	4.50 (0.87)	21.7 (3.19)
200611/01 [29]	0.005% Latanoprost/0.5% timolol	8	IOP Curve (6)	2, 6, 10, 14, 18, 22	10.70 (0.45)	39.34 (1.66)	7.00 (0.49)	30.30 (2.11)	8.60 (0.34)	34.40 (1.36)
200702/01 [30]	2.0% Dorzolamide/0.5% timolol	4	Single (1)	4	6.50 (0.38)	27.08 (1.60)	-	-	-	-
200704/01 [31]	0.2% Brimonidine/0.5% timolol	4	IOP Curve (3)	0, 4, 8	8.20 (0.35)	34.70 (1.46)	7.50 (0.38)	33.90 (1.79)	7.80 (0.35)	34.30 (1.55)
	2.0% Dorzolamide/0.5% timolol	4	IOP Curve (3)	0, 4, 8	7.80 (0.33)	33.20 (1.43)	7.20 (0.37)	32.80 (1.66)	7.40 (0.33)	32.90 (1.57)
200801/01 [32]	2.0% Dorzolamide/0.5% timolol	8	IOP Curve (6)	2, 6, 10	9.50 (0.35)	35.06 (1.30)	5.40 (0.37)	23.18 (1.57)	7.20 (0.29)	28.57 (1.14)
200804/01 [33]	0.03% Bimatoprost/0.5% timolol	6	IOP Curve (3)	0, 2, 8	9.60 (0.16)	37.07 (0.62)	7.70 (0.17)	33.05 (0.73)	8.40 (0.14)	34.29 (0.57)
200808/01 [34]	2.0% Dorzolamide/0.5% timolol	8	IOP Curve (7)	0, 2, 4, 6, 8, 10, 12	5.90 (0.56)	24.48 (2.31)	5.30 (0.56)	21.12 (2.23)	5.80 (0.48)	23.58 (1.95)
200808/02 [35]	2.0% Dorzolamide/0.5% timolol	6	IOP Curve (8)	0, 2, 6, 10, 12	6.60 (0.30)	25.68 (1.17)	3.20 (0.30)	14.68 (1.38)	5.10 (0.30)	20.86 (1.23)
200810/01 [36]	2.0% Dorzolamide/0.5% timolol	6	IOP Curve (12)	0, 2, 4, 6, 8, 10, 12	10.10 (0.35)	37.69 (1.32)	5.40 (0.35)	25.47 (1.66)	7.30 (0.49)	32.16 (2.16)

Table 3. Cont.

Trial	Medication	End point of measurement (weeks)	Type of measurement	Time points (hours after dosing)	Highest (SE)		Lowest (SE)		Diurnal (SE)	
					Absolute (mm Hg)	Relative (%)	Absolute (mm Hg)	Relative (%)	Absolute (mm Hg)	Relative (%)
200810/02 [37]	1.0% Brinzolamide/0.5% timolol	13	IOP Curve (5)	0, 2, 4, 8, 12	8.70 (0.29)	33.72 (1.12)	8.30 (0.30)	30.63 (1.11)	7.56 (0.33)	30.51 (1.33)
200811/01 [38]	0.2% Brimonidine/0.5% timolol	13	IOP Curve (6)	2, 6, 10	6.90 (0.43)	25.65 (1.62)	4.50 (0.36)	19.65 (1.57)	5.30 (0.23)	21.54 (0.92)
200812/01 [39]	0.2% Brimonidine/0.5% timolol	8	IOP Curve (4)	0, 2, 6, 8	7.89 (0.40)	32.93 (1.67)	6.56 (0.37)	28.52 (1.62)	7.02 (0.29)	29.96 (1.24)
	2.0% Dorzolamide/0.5% timolol	8	IOP Curve (4)	0, 2, 6, 8	7.47 (0.44)	30.96 (1.82)	6.56 (0.43)	28.64 (1.85)	6.91 (0.37)	29.49 (1.58)
200904/01 [40]	0.004% Travoprost/0.5% timolol	8	IOP Curve (6)	4, 8, 12, 16, 20, 24	11.30 (0.48)	39.10 (1.66)	7.30 (0.48)	30.04 (1.98)	9.40 (0.38)	35.34 (1.43)
200904/02 [41]	1.0% Brinzolamide/0.5% timolol	13	IOP Curve (3)	0, 2, 8	9.10 (0.35)	34.90 (1.35)	9.10 (0.36)	33.30 (1.32)	9.00 (0.35)	34.62 (1.35)
	2.0% Dorzolamide/0.5% timolol	13	IOP Curve (3)	0, 2, 8	8.80 (0.35)	33.50 (1.34)	8.70 (0.36)	31.60 (1.32)	8.75 (0.35)	33.56 (1.34)
200905/01 [42]	0.005% Latanoprost/0.5% timolol	8	IOP Curve (6)	2, 6, 10, 14, 18, 22	10.20 (0.51)	35.05 (1.76)	7.40 (0.56)	29.84 (2.26)	9.00 (0.47)	34.22 (1.80)
200907/01 [43]	0.2% Brimonidine/0.5% timolol	4	Single (1)	2	7.30 (0.56)	31.74 (2.43)	-	-	-	-
	2.0% Dorzolamide/0.5% timolol	4	Single (1)	2	7.40 (0.63)	31.36 (2.67)	-	-	-	-
200910/01 [44]	0.005% Latanoprost/0.5% timolol	8	IOP Curve (3)	12, 14, 16	10.38 (1.00)	42.09 (4.06)	8.72 (1.18)	38.76 (5.24)	9.35 (1.04)	40.34 (4.49)
200911/01 [45]	0.004% Travoprost/0.5% timolol	6	IOP Curve (2)	0, 7	10.40 (0.25)	38.66 (0.93)	8.90 (0.25)	35.46 (1.00)	9.65 (0.25)	37.06 (0.97)
	2.0% Dorzolamide/0.5% timolol	6	IOP Curve (2)	0, 7	9.30 (0.25)	34.44 (0.93)	8.50 (0.23)	33.86 (0.92)	8.90 (0.24)	34.15 (0.93)
201002/01 [46]	0.005% Latanoprost/0.5% timolol	6	IOP Curve (3)	12, 14, 20	-	-	-	-	10.10 (0.26)	36.07 (0.92)
201007/01 [47]	0.005% Latanoprost/0.5% timolol	12	IOP Curve (3)	12, 16, 20	9.80 (0.20)	36.57 (0.75)	9.60 (0.20)	36.50 (0.76)	9.70 (0.20)	36.47 (0.75)
	2.0% Dorzolamide/0.5% timolol	12	IOP Curve (3)	0, 4, 8	9.70 (0.30)	35.27 (1.09)	9.40 (0.30)	35.21 (1.12)	9.50 (0.20)	34.80 (0.73)
201007/02 [48]	0.005% Latanoprost/0.5% timolol	6	IOP Curve (3)	12, 14, 20	-	-	-	-	10.00 (0.21)	35.59 (0.75)
201102/01 [49]	0.005% Latanoprost/0.5% timolol	4	Single (1)	12	7.73 (0.70)	28.01 (2.55)	-	-	-	-
	0.004% Travoprost/0.5% timolol	4	Single (1)	12	6.56 (0.48)	24.85 (1.81)	-	-	-	-
	0.03% Bimatoprost/0.5% timolol	4	Single (1)	12	8.88 (0.58)	31.71 (2.09)	-	-	-	-

IOP = intraocular pressure; SE = standard error.

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Table 4. Absolute and relative reductions in intraocular pressure.

Group	Time point	Absolute reduction (mm Hg)		Relative reduction (%)		No. of studies
		Mean	95% confidence interval	Mean	95% confidence interval	
Dorzolamide/timolol	Diurnal	7.41	6.69 to 8.12	29.9	27.4 to 32.4	18
	Highest	8.03	7.36 to 8.71	31.3	29.3 to 33.3	19
	Lowest	6.31	5.15 to 7.46	25.9	22.4 to 29.4	15
Brinzolamide/timolol	Diurnal	8.33	6.82 to 9.84	32.7	28.3 to 37.1	2
	Highest	8.86	8.43 to 9.30	34.2	32.5 to 35.9	2
	Lowest	8.68	7.89 to 9.46	31.9	29.3 to 34.5	2
Brimonidine/timolol	Diurnal	6.55	5.59 to 7.40	28.1	23.2 to 32.9	4
	Highest	7.59	7.19 to 7.99	31.5	28.7 to 34.3	5
	Lowest	5.87	4.58 to 7.16	26.1	20.6 to 31.6	4
Latanoprost/timolol	Diurnal	8.85	8.30 to 9.40	33.9	32.5 to 35.2	12
	Highest	9.29	8.67 to 9.91	34.5	32.5 to 36.6	10
	Lowest	7.86	7.02 to 8.70	32.0	29.6 to 34.5	9
Travoprost/timolol	Diurnal	9.09	8.32 to 9.87	34.9	33.0 to 36.8	7
	Highest	9.49	8.66 to 10.32	35.5	32.8 to 38.3	8
	Lowest	7.99	7.34 to 8.65	32.6	30.5 to 34.6	7
Bimatoprost/timolol	Diurnal	8.40	8.13 to 8.67	34.3	33.2 to 35.4	1
	Highest	9.46	8.89 to 10.02	34.8	29.6 to 40.0	2
	Lowest	7.70	7.36 to 8.03	33.1	31.6 to 34.5	1

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which might be a "negative" result because that the data is based on only one single trial [50]. For the highest IOP reduction, travoprost/timolol and bimatoprost/timolol were more effective than dorzolamide/timolol. Latanoprost/timolol and travoprost/timolol were also more effective than dorzolamide/timolol and brimonidine/timolol in the lowest IOP reduction. Therefore, both latanoprost/timolol and travoprost/timolol might achieve better IOP-lowering effects among the six fixed-combination agents.

The overview of relative results of mean diurnal IOP reduction, the highest and lowest IOP reduction found that brinzolamide/timolol achieved an IOP-lowering effect of more than 30%. However, the mixed-effects meta-regression results suggested that there was no significant difference in lowering IOP when comparing brinzolamide/timolol with dorzolamide/timolol and brimonidine/timolol. The pooled data of brinzolamide/timolol are based on only two papers. One trial found that 1% brinzolamide/0.5% timolol was superior in IOP-lowering efficacy to either brinzolamide 1% or timolol 0.5% [37]. The other trial suggested that the IOP-lowering efficacy of brinzolamide/timolol was noninferior to dorzolamide/timolol [41]. Owing to the "small-study effects" with the presence of substantial between-study heterogeneity, it might not be the truly IOP-lowering effect of brinzolamide/timolol.

Table 5. Weighted mean difference in relative intraocular pressure reductions.*

Time Point	Treatment comparison		Weighted mean difference (%)		*P* value
	A	B	Mean	95% confidence interval	
Diurnal	Latanoprost/timolol	Dorzolamide/timolol	3.8	0.8 to 6.7	0.011
	Latanoprost/timolol	Brimonidine/timolol	5.9	2.5 to 9.4	0.001
	Travoprost/timolol	Dorzolamide/timolol	3.3	2.2 to 4.5	0.000
	Travoprost/timolol	Brimonidine/timolol	7.0	2.5 to 11.6	0.003
Highest	Travoprost/timolol	Dorzolamide/timolol	4.2	0.6 to 7.8	0.021
	Bimatoprost/timolol	Dorzolamide/timolol	3.6	2.3 to 5.0	0.000
Lowest	Latanoprost/timolol	Dorzolamide/timolol	6.2	1.4 to 10.9	0.011
	Latanoprost/timolol	Brimonidine/timolol	6.0	0.9 to 11.1	0.021
	Travoprost/timolol	Dorzolamide/timolol	6.7	1.5 to 12.0	0.012
	Travoprost/timolol	Brimonidine/timolol	6.6	1.9 to 11.4	0.006

*For comparisons of treatment A versus treatment B, statistically significant results are shown, and a weighted mean difference above 0 indicates that relative IOP reduction is greater for treatment A than for treatment B.

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A previous meta-analysis including 28 randomized clinical trials evaluated the IOP lowering effects of all commonly used monotherapies in patients with POAG and OHT, and revealed that the relative peak IOP reductions were 33% for bimatoprost, 31% for latanoprost, 31% for travoprost, 27% for timolol, 25% for brimonidine, 22% for dorzolamide, and 17% for brinzolamide [3]. The present meta-analysis found that when using as fixed combinations with timolol, dorzolamide/timolol, brinzolamide/timolol and brimonidine/timolol can result an IOP-lowering effect of more than 30%. However, the relative IOP reductions of the fixed combinations of 0.5% timolol and PGAs were only 34.8% for latanoprost/timolol, 33.0% for travoprost/timolol, and 32.9% for bimatoprost/timolol. One explanation is that with any fixed combination of 0.5% timolol and a PGA, a timolol dose will be omitted, leading to a lower IOP reduction [8,51]. Because timolol has the peak effect approximately 2 hours after dosing, and prostaglandins provide maximal IOP reduction during the last half of the dosing interval (ie, post instillation hours 12 through 24) [52], the peak effect of prostaglandin-timolol fixed combinations might be provided by prostaglandins mostly, but not the combination of prostaglandins and timolol. Another explanation is that the terminology concerning *diurnal* is not consistent in the studies reporting a mean of several IOP measurements during a (part of a) day, and only a limited number of measurements during only a part of a 24-hour period are achieved [8]. Nineteen arms from 18 trials reported a mean diurnal IOP curve of the fixed combination of timolol and a PGA. In 10 arms, all measurements were obtained within 8 hours after dosing, with three moments in 9 trials and two moments in the other one. In 6 arms, measurements were obtained in three moments up to 12 to 24 hours after installation. Full 24-hours IOP measurements were obtained in only 4 trials. If one includes only IOP measurements within a period of 8 hours or fewer after the administration of a combination of timolol and a PGA, the absence of peak efficacy moments of the PGA will lead to an underestimation of IOP-lowering effect [8].

Although we tried to conduct a thorough review of the existing literature, this present analysis has limitations inherent to any systematic review. First, a limitation of this meta-analysis is that only published studies were included. Although multiple databases and websites were searched, unfortunately, it is possible that we may have failed to include some papers, especially those published in other languages. A specific limitation of this analysis is that many trials lacked adequate allocation concealment, blinding, sample size assessment, and intention-to-treat analysis, which may leave them vulnerable to bias and misestimation of the beneficial effects of IOP-lowering agents. Finally, the pooled data of bimatoprost/timolol and brinzolamide/timolol are based on only two papers. Therefore, more research is still needed on the available guidance derived from the currently literature.

Lowering IOP is beneficial in both POAG and OHT. Depending on the glaucomatous damage and the presence of other risk factors, the target IOP often has to be chosen such that IOP lowering beyond 30% or even 40% is necessary. However, the maximum mean IOP reduction from baseline IOP was 33% in the case of monotherapy [3]. Therefore, the fixed-combination medications are needed to reach these low target IOP levels, which not only provide better IOP-lowering effects, but also improve compliance and eliminate the washout effect.

In conclusion, the results of this systematic review suggest that all six commonly used fixed-combination drugs containing timolol can effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travoprost/timolol might achieve better IOP-lowering effects among the six fixed-combination agents.

Author Contributions

Conceived and designed the experiments: JWC SWC LDG GCL RLW. Performed the experiments: JWC SWC LDG GCL RLW. Analyzed the data: JWC SWC GCL. Contributed reagents/materials/analysis tools: JWC SWC RLW. Wrote the paper: JWC SWC LDG GCL RLW.

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REVIEW ARTICLE

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Prostaglandin Analogues in the Treatment of Glaucoma

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Contents

Abstract

Prostaglandin (PG) analogues are a new class of ocular hypotensive drugs that have been developed for the treatment of open angle glaucoma. Two of these drugs, latanoprost and unoprostone, are presently commercially available.

Latanoprost was introduced in 1996 in the US and Europe. Presently it enjoys the most widespread use and is the most well documented drug of this group. It reduces the intraocular pressure (IOP) by a mechanism of action different from other drugs; namely by increasing the uveoscleral outflow. The aqueous inflow

is not affected. The optimal dose regimen is one drop of 50 μg/ml once daily, which reduces the IOP by approximately 30% in patients with glaucoma. A more pronounced ocular hypotensive effect is demonstrated when latanoprost is combined with other glaucoma therapies, including β-blockers, adrenergic and cholinergic agonists or carbonic anhydrase inhibitors. Latanoprost is well tolerated. The drug reaches a plasma concentration below that needed for stimulation of the FP-receptor, which may explain its favourable systemic tolerability profile. The major ocular adverse effect is increased iris pigmentation, which is due to increased synthesis of melanin in the melanocytes of the iris stroma. It is most frequently seen in green-brown eyes and it is probably permanent. A low frequency of cystoid macular oedema has also been reported, predominantly in predisposed eyes.

Unoprostone was launched in Japan in 1994, but there is little experience with this drug outside the Japanese market and the documentation is more limited. Its main mechanism of action is on outflow, but this is not yet fully elucidated. The recommended dosage regimen is 1 drop of 1.2 mg/ml twice daily. No comparative studies in humans between the 2 drugs have yet been published.

A new class of ocular hypotensive agents, prostaglandin (PG) analogues, has been developed for the treatment of glaucoma. Two preparations for topical use are presently commercially available. In 1994, isopropyl unoprostone was launched on the Japanese market. Two years later latanoprost was introduced in the US and in many European countries. The purpose of this article is to give the rationale for the use of PG analogues in the management of glaucoma and to report the present clinical experience with these drugs.

1. Glaucoma and Glaucoma Treatment

Glaucoma is a major cause of blindness all over the world. It is reported to be the second most common cause in the US and the most frequent in the Black population.[1,2] Glaucoma can be divided into several clinical entities of which primary open angle glaucoma (POAG) is the most common.[3] In the Scandinavian countries the pseudoexfoliation glaucoma is often added to this group.

Glaucoma may be defined as a progressive optic neuropathy with characteristic changes of the optic nerve head and the visual field. Elevated intraocular pressure (IOP) is an important risk factor that aggravates the course of the disease. Other mechanisms such as neurotoxicity or impaired blood circulation may contribute to the damage, but the only risk factor amenable to therapeutic intervention today is the IOP.

IOP is maintained by the balance between inflow and outflow of aqueous humour in the eye (fig. 1). Aqueous humour is produced by the non-pigmented ciliary epithelium in the ciliary body and it escapes from the eye at the irido-corneal angle. A major drainage route is via the trabecular or conventional route, i.e. through the trabecular meshwork, into Schlemm's canal, collector channels, aqueous veins and, finally, the general venous circulation. Another route is the uveoscleral or unconventional route,[4] i.e. across the iris root and the ciliary muscle, through the connective tissue between the muscle bundles, into the suprachoroidal space and out through the sclera.

The elevated IOP is the result of an impaired outflow of aqueous humour but treatment, both surgical and medical, can be aimed at inflow as well as outflow. Surgical treatments affecting inflow include all cyclodestructive procedures. Filtering procedures as well as laser trabeculoplasty aim at increasing outflow. β-blockers, α-agonists and carbonic anhydrase inhibitors suppress aqueous humour production. Cholinergic and adrenergic agonists increase trabecular outflow. PGs are the first drugs where the main effect on IOP is caused by increased uveoscleral outflow.[5-11]

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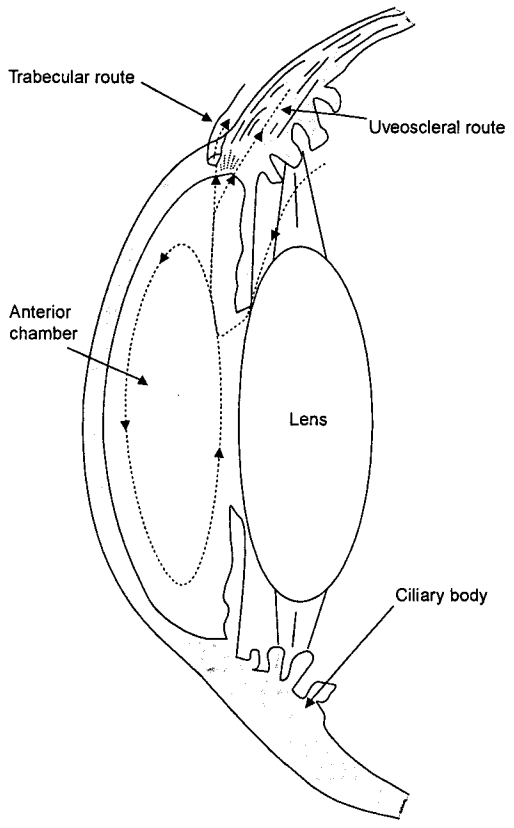

Fig. 1. Anterior segment of the eye with aqueous humour circulation indicated.

2. Brief Prostaglandin (PG) Pharmacology

Eicosanoids can be defined as the further metabolic products of arachidonic acid, a polyunsaturated fatty acid (straight chain C-20 carboxylic acid). PGs constitute a group of naturally occurring hydroxylated fatty acids, found in small concentrations in mammalian tissues. They are characterised by high pharmacological potency and a diverse spectrum of biological activities. The biological properties of the various PGs are mainly dependent on the oxidation state of the cyclopentane ring. They are biosynthesised from free arachidonic acid, which is released from membrane phospholipids after activation of phospholipase A_2 or C by a variety of physiological stimuli. They do not appear to be stored free in tissues, but they are biosynthesised and released on demand. PGs together with thromboxanes and leukotrienes constitute the principal eicosanoids. Thromboxane (TXA_2) is another metabolite of arachidonic acid, which is classified as a PG. However, strictly speaking it is not a PG since the prostanoic acid cyclopentane ring is missing. Naturally occurring PGs, $PGF_{2\alpha}$, PGE_2, PGD_2 and prostacyclin (PGI_2) together with TXA_2 are designated as prostanoids.

The last letter of the abbreviations of the naturally occurring PGs (e.g. F) refers to the ring structure, while the figure in the subscripts refers to the number of double bonds. The Greek letter subscript refers to the orientation of the hydroxyl groups, above or below the plane of the ring. Thus, $PGF_{2\alpha}$ derives from arachidonic acid, has 2 double bonds, 1 in each side chain and has its hydroxyl groups below the plane.

PGs are not metabolised locally but released into the circulation. In the eye, inactivation of PGs is a result of removal of PGs from the eye by outward-directed active transport systems in the blood-ocular barriers.[12] PGs reaching the circulation are rapidly inactivated, mainly during their passage through the lung,[13] and the plasma half-life ($t_{1/2}$) of most PGs is <1 minute.[14] However, the $t_{1/2}$ of latanoprost is 10 minutes in monkeys[11] and 17 minutes in humans (B. Sjöquist, personal communication, 1997). Latanoprost is mainly inactivated in the liver, and while most of the metabolites are excreted in the urine, a minor part is eliminated in the faeces.[11]

2.1 PG Receptors

The diversity of the effects of PGs is explained by the existence of a number of different prostanoid receptors. The receptors are named DP-, EP- (4 subtypes), FP-, IP- and TP-receptors for the natural PG (PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 or TXA_2) for which they have the greatest affinity.[15] All natural PGs have affinity for more than 1 receptor resulting in a mixed pharmacological response. Thus, selective agonists or antagonists can be expected

to have more specific effects than naturally occurring PGs.

The FP receptor has a widespread distribution within the tissues of the eye including the ciliary muscle and the ciliary processes.[16]

2.2 Brief History of PGs

In 1930, 2 American gynaecologists, Kurzrok and Lieb,[17] observed that the human uterus muscle contracted when it was exposed to seminal fluid. Goldblatt[18,19] in England and von Euler[20] in Sweden independently verified that seminal fluid contracted smooth muscle. Von Euler[20] identified 2 substances which he called PGs as he assumed they derived from the prostate. One was soluble in ether and the other in phosphate (that is 'fosfat' in Swedish). Consequently, they were named prostaglandins E and F. The name prostaglandin has been retained although it was discovered that the 2 PGs did not originate from the prostate gland, but from the seminal vesicles and that PGs were also generated from a variety of other tissues.

Ambache[21,22] made the first observation of PG effects in the eye. He isolated a substance in iris extracts capable of contracting the cat iris. It was named irin. It was later shown that irin was a mixture of PGs, mainly $PGF_{2\alpha}$ and PGE_2.[23-25]

2.3 Early Animal Experiments

In an early attempt to administer PGs topically, PGE_1 was applied to rabbit eyes in doses from 0.5 to 50 μg and caused a dose-dependent increase in IOP, hyperaemia and breakdown of the blood-aqueous barrier (BAB).[26] Later, it was reported that a topically applied low dose of another PG, $PGF_{2\alpha}$ 0.5μg, gave a reduction in IOP in the rabbit eye lasting for several hours.[27] Subsequent studies have confirmed that $PGF_{2\alpha}$[28] as well as PGE_2, PGD_2,[29] PGE_3 and PGD_3[30] reduce IOP in the rabbit eye. Persistent IOP reduction was shown also for $PGF_{2\alpha}$ and PGE_2 in normo- or hypertensive eyes of several species including cats, dogs and monkeys.[6,28,31-36]

2.4 Early Human Studies

The first report on the ocular effects of topically applied $PGF_{2\alpha}$ (fig. 2) in volunteers was published in 1985.[37] 200 μg of the tromethamine salt (dinoprost) reduced IOP significantly for 4 to 24 hours in normotensive eyes, but caused marked hyperaemia, ocular pain and headache.

With the purpose of reducing the adverse effects and to increase the bioavailability, $PGF_{2\alpha}$ was made more lipid-soluble by esterification of the carboxyl group.[38] $PGF_{2\alpha}$-isopropyl ester ($PGF_{2\alpha}$-IE) penetrates the corneal epithelium more readily and can be used in much lower doses than the tromethamine salt. It is hydrolysed to $PGF_{2\alpha}$ during its passage through the cornea by the enzymes, butyryl-cholinesterase and carboxylesterase.[39,40]

In the first study performed on healthy volunteers 1 to 10 μg of $PGF_{2\alpha}$-IE was found to reduce

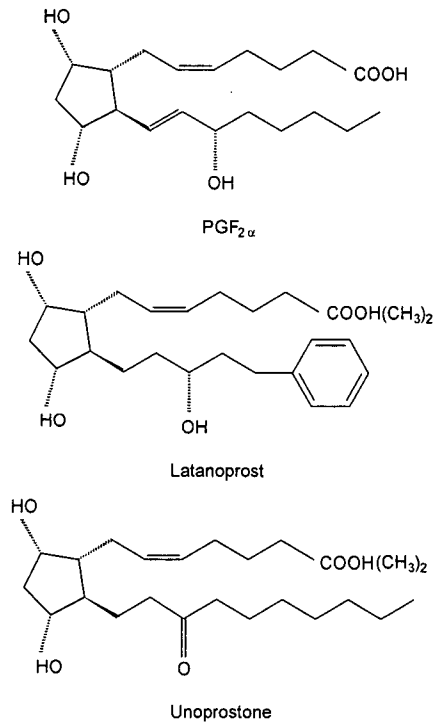

Fig. 2. Structural formulas of prostaglandin (PG) $F_{2\alpha}$, latanoprost and unoprostone.

IOP in a dose-dependent manner, but the adverse effects were still a problem with the higher doses.[41] A diester was also tried, but it did not improve the therapeutic index.[42]

3. Latanoprost

In the attempts to find a more selective FP-receptor agonist, a part of the omega chain was substituted with a phenyl-ring. The result was PHXA34, the mixture of the 15-R and 15-S epimers of latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE; PHXA41) [fig. 2]. Latanoprost is the pure 15-R epimer, which is about 10 times more biologically active than the 15-S epimer.[43] Therefore, twice the dose of PHXA34 is required to reach an effect similar to that of latanoprost.

Latanoprost is a biologically inactive prodrug. It is hydrolysed to its active form in cornea or in plasma. About 1% of topically applied latanoprost enters the monkey eye.[11] In human aqueous humour a peak concentration is reached approximately 2½ hours after application.[44]

Latanoprost is a more selective FP-receptor agonist than $PGF_{2\alpha}$[11] and this has resulted in an improved therapeutic profile with much less hyperaemia and negligible irritation compared with $PGF_{2\alpha}$ and a retained IOP lowering effect.[45-47]

The drug concentration in a vial of latanoprost (50 μg/ml) is about 10^{-4} mol/L, whereas in aqueous humour and in plasma the peak concentrations reach about 10^{-7} mol/L and 10^{-10} mol/L, respectively.[44] The EC_{50} for the affinity of latanoprost to the FP-receptor is 3.6×10^{-9} mol/L.[11]

3.1 Dose

The optimal latanoprost concentration for reducing IOP in volunteers has been found to be about 50 μg/ml, i.e. 0.005%.[48-50] The maximum IOP reduction is seen 6 to 12 hours after the administration of a single drop.[49,51]

Once daily administration is superior to twice daily with regard to the ocular hypotensive effect during the day (i.e. the IOP remains higher with twice daily administration compared with once daily).[52-55] The mechanism behind this is not completely understood. A likely explanation may be a true reduction of the efficacy of latanoprost by development of subsensitivity.[55]

3.2 Mechanism of Action

Latanoprost reduces IOP in monkeys by increasing uveoscleral outflow.[11] An increase of 60% in uveoscleral outflow was found after the application of latanoprost 3μg daily for 5 days, whereas trabecular outflow was unchanged.[11] This confirms the previous results from studies of $PGF_{2\alpha}$[5,6] and $PGF_{2\alpha}$-IE[7-9] in monkeys. There is also indirect evidence to support the same mode of action of latanoprost in humans.[10] The exact mechanism behind the increase in uveoscleral outflow is not known, but latanoprost is able to induce transient changes in the extracellular matrix of the ciliary muscle.[56-59] Such an effect could explain the fact that IOP is not restored to pretreatment levels until 2 to 3 weeks after withdrawal of treatment.[54]

Neither $PGF_{2\alpha}$, $PGF_{2\alpha}$-IE or latanoprost reduce aqueous inflow in monkeys[6,7] or in humans.[10,51,60,61]

3.3 Therapeutic Use

3.3.1 Intraocular Pressure (IOP)

Short term use of latanoprost 1 to 4 μg once or twice daily reduced the IOP by 19 to 38% in initial clinical trials in healthy volunteers[49] and in patients with ocular hypertension and glaucoma.[50,62] In subsequent long term studies (6 months or more) in patients where latanoprost was administered once daily the diurnal IOP was reduced 27 to 34% without evidence of loss of effect.[45-47,63,64] Similar results were obtained in a 3-month study.[65] Latanoprost also reduces IOP during the night.[66]

3.3.2 Ocular Blood Flow

Ocular blood flow in the anterior uvea of cynomolgus monkeys, measured with labelled microspheres, increases after topical application of $PGF_{2\alpha}$.[67] However, topical administration of latanoprost 6μg in each eye, i.e. about 4 times the clinical dose, showed an increase in the blood flow

only in the anterior part of the sclera, and no effect was seen in the iris, ciliary body, choroid or retina.[11] Nicolela et al.[68] found no effect on velocity through the retrobulbar vessels determined with colour Doppler velocimetry after topical application of latanoprost.

3.3.3 Combination Therapy

Combinations of drugs are commonly used in glaucoma treatment. Combining a drug that facilitates outflow with one that reduces inflow is a rational approach.

β-Blockers

Several studies have demonstrated the efficacy of combining $PGF_{2\alpha}$-IE or latanoprost with adrenergic β-receptor blockers.[53,69-71] In a 2-week study the effect of latanoprost 0.006% twice daily alone and in combination with timolol 0.5% or vice versa was evaluated. IOP was reduced 31 or 24% by latanoprost or timolol alone. The combinations gave a further reduction of 13 to 14%.[71] Latanoprost 0.006% once or twice daily added to eyes treated with timolol 0.5% yielded an additional reduction in IOP of 37 and 28% respectively after 3 months.[53] The discrepancy in effect between these studies might be explained by different baseline IOPs, study populations, study length and number of patients.

Cholinergic Agonists

When combining latanoprost and cholinergic agonists an antagonistic effect might theoretically be expected, as the cholinergic agonists contract the ciliary muscle. In cynomolgus monkeys, pretreatment with pilocarpine was found to prevent the ocular hypotension produced by $PGF_{2\alpha}$.[5] However, studies in the same species where pilocarpine is administered after PGs are equivocal.[7,72]

In patients with ocular hypertension or glaucoma, topical application of latanoprost 0.006% twice daily, and pilocarpine 2% three times daily, provided a small additive effect.[73] IOP was reduced a further 7 to 14% compared with either drug given alone. This is probably due to the short-lasting effect of the cholinergic drug on the ciliary muscle.[74] In a study in young healthy volunteers,[75] frequent doses of physostigmine did not prevent the ocular hypotensive effect of latanoprost and the effects on IOP were mainly additive. When latanoprost was applied to the eyes of patients with glaucoma receiving maximal tolerated medical treatment, the IOP reduction was similar in eyes receiving cholinergic agonists and eyes not receiving cholinergic agonists.[76]

Adrenergic Agonists

In a short term study in patients with ocular hypertension or glaucoma,[77] latanoprost 0.005% once daily was added to dipivefrine 0.1% twice daily or vice versa. An additional reduction in IOP of 19 or 16% was observed. No effect on the permeability to proteins of the BAB was detected with either drug alone or in combination.

Carbonic Anhydrase Inhibitors

Oral carbonic anhydrase inhibitors are effective in reducing aqueous inflow and are expected to be additive to latanoprost. This was confirmed in a study which added latanoprost 0.005% once daily to oral acetazolamide 250mg twice daily.[78] Acetazolamide alone reduced the IOP by 18 to 23% and a further reduction of 15% was seen when latanoprost was added.

3.3.4 Maximal Tolerated Medical Therapy

The effect of latanoprost in patients with glaucoma already receiving maximal tolerated medical therapy has been reported. An additional IOP reduction of about 23% was seen 1 and 3 months after latanoprost 0.005% was added to existing glaucoma therapy in 24 patients.[79] In approximately 25% of the patients, a target level of a reduction greater than 20% of the baseline IOP was reached. In a longitudinal study of 160 patients with inadequately controlled glaucoma, latanoprost 0.005% produced a significant reduction in IOP in approximately one-third of the patients.[76]

3.4 Adverse Effects

3.4.1 Systemic

The peak concentration of latanoprost in plasma (C_{max}) after topical application of 1 drop of latanoprost 50 μg/ml is approximately 10^{-10} mol/L,[44]

and the $t_{1/2}$ is short, only about 17 minutes. The C_{max} is approximately one tenth of the EC_{50} for the affinity of latanoprost to the FP-receptor, and subsequently systemic adverse effects are unlikely to occur because of the low plasma concentrations.

Respiratory

Large doses of $PGF_{2\alpha}$ are known to constrict the bronchi in humans.[80] This effect is mediated predominantly by TP-receptors.[81] The affinity of latanoprost to the TP-receptor is small[11] and bronchospasm is, therefore, unlikely to occur in patients treated with topical latanoprost. This is supported by a study by Hedner et al.[82] where topical ocular administration of latanoprost, at doses up to approximately 7 times the daily dose (3μg) recommended in bilateral glaucoma treatment, had no effect on pulmonary function in healthy volunteers or in patients with stable moderate intrinsic asthma.

Cardiovascular

In phase III clinical trials,[45,46,47,63] blood pressure and heart rate were determined 12 to 24 hours after topical application of latanoprost. At that time, serum concentrations can be expected to be zero (see section 3.4.1). No consistent effects on these cardiovascular parameters were seen in these phase III trials.

3.4.2 Ocular

Hyperaemia

Hyperaemia was a major problem with the tromethamine salt of $PGF_{2\alpha}$[37] and was still notable when high doses of $PGF_{2\alpha}$-IE were used.[41,83,84] Latanoprost causes less hyperaemia than the naturally occurring $PGF_{2\alpha}$, but slightly more than timolol.[45-47] It was reported as an adverse event in 2 of 183 patients with ocular hypertension or glaucoma in 1 study,[45] which indicates that hyperaemia can be clinically significant in a small group of patients.

Punctate Epithelial Keratopathy

The frequency of punctate epithelial erosions was 7 to 13% in eyes treated with latanoprost 0.005% once daily compared with 2 to 18% in eyes treated with timolol 0.5% twice daily in several studies.[45-47] In these studies, the preservative benzalkonium chloride, 0.02% in latanoprost eye drops (and in the placebo drops) and 0.01% in timolol eye drops, may have contributed to the damage. This hypothesis is supported by an 18-month follow-up study,[64] in which latanoprost was administered once daily and the placebo drops, containing preservative, were discontinued. The frequency of punctate epithelial erosions declined from 13 to 8%.

Blood-Aqueous Barrier

Breakdown of the BAB has been observed in rabbits after topical application of PGs,[27,28] whereas the BAB in monkeys seems to be much more resistant.[6,33] In rabbits, the breakdown is mediated by the EP_2-receptor.[85] No significant BAB breakdown as measured by intraocular protein content has been noted during treatment with latanoprost in human eyes during several studies of up to 6 weeks duration,[49,60,86] and for up to a year in 1 study.[54]

Using slit-lamp examination, a slight flare was noted in less than 2% of patients, and a few cells in the anterior chamber were occasionally present in 5% of patients, during 1 year of latanoprost 0.005% once daily therapy.[63]

It is noteworthy that in clinical studies only selected patients are treated. More uncommon adverse effects or adverse events in more susceptible patients are expected when the drug is used in a larger population. Cystoid macular oedema (CME) was observed in a patient with pseudophakia and a previous history of CME.[87] In a retrospective review of 94 patients with glaucoma treated with latanoprost,[88] anterior uveitis was reported in 8 eyes of 6 patients and CME in 2 eyes of 2 patients. All but one of these eyes had concurrent ocular hypotensive medication. Both eyes with CME and 6 of 8 eyes with anterior uveitis had an intraocular lens implanted. Within 1 week after discontinuation of latanoprost the anterior uveitis in all eyes was resolved. Although a causal relationship between latanoprost treatment and iritis or CME has not been established, some precaution is advocated when patients at potential risk, e.g. patients with

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aphakia or patients with a prior history of uveitis or CME, are treated.

Pigmentation of Iris and Eyelashes

Iris pigmentation was evaluated in a survey[89] of patients included in phase III clinical studies.[45-47] Increased pigmentation of the iris was seen in 12, 23 and 11% of patients in the US, UK and Scandinavia, respectively, after 1 year of latanoprost treatment. The different incidences seen in these populations, probably reflect the different iris colours in the populations. Green-brown eyes are most susceptible to increased pigmentation, followed by yellow-brown and blue-brown eyes. Effects in uniformly coloured eyes are the least likely to be noticed, but unilateral treatment can disclose increased iris pigmentation even in brown eyes. Iris naevi and freckles do not change.

The change in colour has been demonstrated to be the result of an increased synthesis of melanin, i.e melanogenesis, in the melanocytes of the iris stroma, without proliferation of these or other iridial cells.[90] This effect seems to be a class effect since it is seen also with the natural occurring PGs $PGF_{2\alpha}$ and PGE_2.[91] There is no indication that the iris pigmentation has anything but cosmetic consequences but it is likely to be permanent. Melanocytes of the iris are continent, i.e. they do not release their melanin.[92] In patients followed for 2 years after cessation of treatment, no change in iris pigmentation was seen and no pigment dispersion into the anterior chamber was observed.[89]

In the Scandinavian phase III study,[45] 1 patient with darkening of the eyelashes was reported. This adverse effect seems to be more frequent in clinical practice than the phase III studies indicated and careful inspection of eyelashes have shown that longer and darker eyelashes are not uncommon after latanoprost treatment.[93,94] The increased pigmentation is likely to be a result of stimulation by latanoprost of melanin synthesis as well as transfer of melanosomes to hair keratinocytes.[93]

Allergy

Allergic reactions during latanoprost treatment are fairly uncommon. Only 1% of 272 patients evaluated after 1 year's treatment experienced allergic reactions.[63] When latanoprost was used as adjunctive therapy in 160 patients with inadequately controlled glaucoma receiving maximal tolerated medical therapy, 5% developed ocular allergy or irritation requiring cessation of treatment.[76] Many of these patients had previous allergic reactions.

4. Unoprostone

Unoprostone (isopropyl unoprostone; 20-ethyl-13,14-dihydro-15-keto-$PGF_{2\alpha}$-isopropyl ester; UF-021) is another analogue based on $PGF_{2\alpha}$ (fig. 2). In contrast to latanoprost, it has been reported that unoprostone only has a weak agonist activity for FP-receptors and almost no affinity for EP_1 and EP_2 receptors.[95] There is little experience with unoprostone outside the Japanese market and only limited documentation on this drug is at present available in English.

4.1 Dose

Topically applied unoprostone reduces IOP in rabbits in a dose dependent fashion with doses from 0.03 to 0.24%.[96] In addition, in healthy volunteers a dose dependent reduction of IOP has been established with doses of unoprostone 0.03 to 0.12%.[97] The duration of action is shorter than with latanoprost and the recommended dose is 1 drop of 0.12% applied twice daily.

4.2 Mechanism of Action

The main mechanism of action of unoprostone is on outflow, but is not yet fully understood. In rabbits, it is primarily considered to be facilitation of conventional outflow, but uveoscleral outflow may also be involved.[98] In the eyes of healthy volunteers, a single installation of unoprostone 0.12% reduced the IOP without affecting aqueous flow, outflow facility or episcleral venous pressure.[99] Similar results were obtained in another study where an increase of unconventional outflow was suggested as the possible mechanism of IOP reduction with unoprostone.[100]

4.3 Therapeutic Use

4.3.1 Effects on IOP

The IOP reducing effect of unoprostone has been examined in a number of studies. The Japanese population has a lower normal IOP than Caucasians, which has to be considered when studies in these different populations are compared. In a multicentre (n = 18) Japanese study,[101] 158 patients with POAG or ocular hypertension were randomised to either unoprostone 0.12% twice daily or timolol 0.5% twice daily for 12 weeks. From the baseline value of 23.5mm Hg the mean reduction of IOP was 5.1mm Hg (22%) in unoprostone treated eyes 4 hours after drop instillation. These values are likely to be close to the peak effect. A similar reduction was seen in eyes treated with timolol. In another study,[102] 114 patients with POAG or ocular hypertension were randomised to receive 1 drop of either unoprostone 0.06 or 0.12% twice daily for 1 year. The mean reduction of the IOP was 16 to 19% in eyes treated with 0.12% unoprostone and less in eyes treated with 0.06%.

No comparative studies in humans between latanoprost and unoprostone have yet been published. However, in monkeys with glaucoma, latanoprost seemed to be more potent than unoprostone in reducing IOP in 1 study.[103]

4.3.2 Combination Therapy

In a study in 7 patients with glaucoma,[104] it was concluded that a combination of unoprostone 0.12% twice daily plus timolol 0.5% twice daily was more potent in reducing the IOP than either drug alone. The IOP reductions were 3.3, 3.0 and 4.6mm Hg for unoprostone, timolol and the combination, respectively. In some patients with refractory glaucoma a beneficial effect of additional unoprostone has been reported.[105]

4.4 Ocular Adverse Effects

In 2 clinical studies (reported together),[102] a total of 193 patients receiving unoprostone 0.06% or 0.12% for 12 or 52 weeks, conjunctival hyperaemia was reported in 4 to 12% and corneal erosions in 3 to 5% of patients. These were the 2 most frequent ocular adverse effects. In another study,[106] 96 eyes of an inhomogeneous glaucoma population were treated for an average of 5.4 months. Severe corneal defects and little effect on the IOP were found in patients with diabetes mellitus. Blepharoconjunctivitis was common among eyes with a history of intraocular surgery. Some fluctuation of flare intensity was also noted.

Unoprostone has been tested mainly in eyes with a homogenous brown iris. One patient with increased pigmentation has been reported.[107] The effect on iris pigmentation in a mixed population is not known. As noted in section 3.4.2, the increase in iris pigmentation seems to be a class effect for PGs and studies in eyes with mixed colours are needed before an evaluation of the effect of unoprostone on iris pigmentation can be made.

5. Future Prospects

PG analogues are a recent contribution to the treatment of open angle glaucoma. They have only been available for a few years, but the results so far are very promising. They have demonstrated that IOP can be effectively reduced by modification of the uveoscleral outflow route. This opens up a new line of research and further studies on the mechanism of action of PGs may give information that can provide even more effective drugs. The advantage of modification of the uveoscleral outflow route is obvious. Unlike drugs that reduce aqueous inflow or increase conventional outflow, drugs that increase uveoscleral flow may reduce the IOP to levels close to or even below the episcleral venous pressure. Thus, the PG analogues have shown that it is possible medical treatment may become as effective as surgery in terms of IOP reduction.

6. Conclusions

PGs analogues constitute a new class of glaucoma drugs with a main mechanism of action different from other drugs currently used in this indication. Latanoprost is the PG analogue that is currently most widely used and its use is the most well documented. It is highly efficient in reducing

the IOP and severe adverse effects seem to be rare. Since its introduction, approximately 1 000 000 patients have been treated with latanoprost[108] and available experience suggests that PG analogues may have the potential to become one of the drugs of first choice for certain patients with open angle glaucoma. The use of unoprostone is less well documented and for the time being it is commercially available only in Japan, where more than 250 000 patients have been treated with the drug. No comparative studies in humans have yet been published, but available data indicate that unoprostone may have a smaller effect on IOP than latanoprost.

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Bimatoprost and Travoprost: A Review of Recent Studies of Two New Glaucoma Drugs

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Abstract. Bimatoprost (Lumigan™ [Allergan, Inc, Irvine CA]) and travoprost (Travatan™ [Alcon, Ft Worth, TX]) are two new intraocular pressure (IOP)-lowering drugs for use in patients with glaucoma and ocular hypertension. This review evaluates recent studies comparing these new drugs with timolol and with latanoprost. In each study, the statistical analyses support the conclusion that these agents were more effective than timolol and as effective as latanoprost in terms of their ability to reduce IOP. The side effect profiles for bimatoprost, latanoprost, and travoprost were similar, but with statistically higher occurrences of hyperemia and eyelash growth for bimatoprost or travoprost versus latanoprost or timolol. (**Surv Ophthalmol 47(Suppl 1)**:S105–S115, 2002. © 2002 by Elsevier Science Inc. All rights reserved.)

Key words. bimatoprost • glaucoma • intraocular pressure • ocular hypertension • latanoprost • timolol • travoprost

Bimatoprost (Lumigan™ [Allergan, Inc, Irvine CA]) and travoprost (Travatan™ [Alcon, Ft Worth, TX]) are two new intraocular pressure (IOP)-lowering drugs for use in patients with glaucoma and ocular hypertension. Bimatoprost has been described as a prostamide.[50] Recent publications have compared this drug with timolol (Timoptic™ [Merck, West Point, PA]),[4,27,40] a beta-adrenergic antagonist, and latanoprost (Xalatan™ [Pharmacia, Peapack, NJ]),[16,19] a prostaglandin (PG) $F_{2\alpha}$ analog. Travoprost is a $PGF_{2\alpha}$ analog, selective for the FP prostanoid receptor, similar to fluprostenol or latanoprost.[22,23] Fluprostenol is a prototypical selective FP agonist, first described in the 1970s.[13,17] Travoprost has been compared with timolol[20,33] and latanoprost[33] in clinical trials of ocular hypertensive and glaucoma patients. This review summarizes the recently published clinical studies of the efficacy, adverse effects, and ocular hypotensive mechanism of action of bimatoprost and travoprost.

Bimatoprost

CHEMICAL STRUCTURE

Bimatoprost (AGN 192024), (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, has a chemical structure (Fig. 1) similar to $PGF_{2\alpha}$ analogs, although it reportedly is not a PG and does not act on prostanoid receptors.[50] However, a recent study has demonstrated binding of bimatoprost to the FP prostanoid receptor,[39] which is the same receptor selectively activated by latanoprost. The free acid of bimatoprost is identical to that of latanoprost with the exception of a double instead of single-bond at the carbon 13-14 position. The free acid of bimatoprost is known to be a very potent FP receptor agonist.[36,37,41,42] The hydrolysis of bimatoprost has been demonstrated in human corneal tissue in vitro.[30] Enzymes, including amidases, peptidases, and fatty acid amide hydrolases, capable of hydrolyzing bimatoprost to its free

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acid have been demonstrated in mammalian tissues, including the brain, kidney, liver, lung, and several ocular tissues.[29] Amides, such as anandamide,[29,35] and amide prodrugs, such as nepafenac[25] and prostanoid DP receptor agonists,[22] have been shown to be hydrolyzed to their free acids by ocular tissues. Given the above findings, it is plausible that bimatoprost is hydrolyzed to its free acid and activates FP prostanoid receptors when used in glaucoma therapy.[7]

OCULAR HYPOTENSIVE MECHANISM OF ACTION

Topical eye drops used to treat glaucoma may lower IOP by reducing the production rate of aqueous humor, by increasing the facility of aqueous outflow through the trabecular meshwork, by increasing the drainage of aqueous humor through the uveoscleral outflow pathway, or by decreasing the pressure within the episcleral veins. Some ocular hypotensive drugs have effects on several of these parameters.[45,49]

The ocular hypotensive mechanism of action of bimatoprost was reported in a clinical study of 25 ocular normotensive volunteers.[5] One eye was treated with bimatoprost 0.03% and the contralateral eye was treated with vehicle once daily for 3 days. Compared with the vehicle-treated eyes, the bimatoprost-treated eyes had a 20% reduction in IOP, 13% increase in aqueous humor flow, and 26% increase in outflow facility as measured by Schiötz tonography. The outflow facility increase (or outflow resistance decrease) was insufficient to account for the entire IOP reduction, suggesting that either uveoscleral outflow (pressure insensitive outflow) was increased or episcleral venous pressure (extraocular recipient pressure) was decreased.

These effects of bimatoprost on aqueous humor dynamics are consistent with those of $PGF_{2\alpha}$ analogs. Latanoprost increased outflow facility in a clinical study[52] performed by the same group that reported a bimatoprost-induced increase in outflow facility.[5] Other clinical studies also report an increase in outflow facility with several $PGF_{2\alpha}$ analogs.[3,10,28] An aqueous flow increase has been reported in monkeys treated with $PGF_{2\alpha}$-tromethamine salt[15] and $PGF_{2\alpha}$-isopropyl ester[34] and in ocular normotensive volunteers treated with latanoprost.[31] Neither latanoprost[44] nor unoprostone[38] had an effect on episcleral venous pressure. Most studies of prostaglandins and their analogs that have investigated uveoscleral outflow have reported an increase.[45]

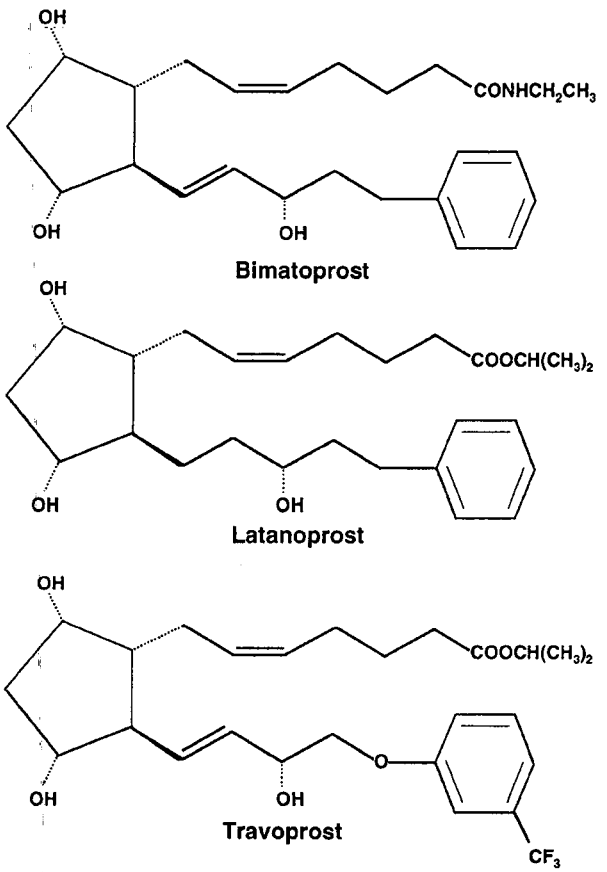

Fig. 1. Chemical structure of bimatoprost, latanoprost, and travoprost.

BIMATOPROST VERSUS TIMOLOL

30-Day Trial

One hundred patients, with primary open-angle glaucoma or ocular hypertension (IOPs between 23 and 34 mm Hg), were randomized into five treatment groups of 20 patients each: bimatoprost 0.003%, 0.01%, 0.03%, bimatoprost vehicle, and timolol 0.5% (Table 1).[27] Diurnal IOP measurements were obtained at 8 AM, 12 noon, 4 PM, 8 PM, and 10 PM on days 0, 14, 21, and 28. IOP was measured at 8 AM only on days 3, 7, 23 and 30 (two days after the last treatment). Bimatoprost was given once per evening (between 7:30 and 9:30 PM) for the first 21 days, and then twice-daily (between 7:30 and 9:30 AM in addition to the PM dose) for seven additional days. For the 28 days, vehicle and timolol were given twice-daily at the times indicated for twice-daily bimatoprost. Mean change in IOP from baseline was the primary efficacy variable. The mean IOP of both eyes was considered the unit of response.

At 8 AM, the bimatoprost 0.03% group but not the vehicle group exhibited statistically significant reductions in IOP from baseline. Bimatoprost 0.03% reduced IOP more than timolol at 5 of the 6 treatment visits (days 3, 7, 14, 23, and 28). No statistically significant difference was found at day 21 at 8 AM.[27] A persistent IOP effect was found two days following the final dose, at which time IOP was reduced from baseline by 5.6 mm Hg in the bimatoprost group and by 2.1 mm Hg in the timolol group ($p = 0.02$).

TABLE 1

Summary of IOP Results From Published Studies Comparing Bimatoprost or Travoprost to Timolol and/or Latanoprost

Study	Drug/Vehicle and Concentration	Primary Outcome	n	Duration of Treatment	Administration[a]	Baseline IOP (mm Hg)	IOP Change from Baseline (mm Hg)[b]	% IOP Change from Baseline[b]
Laibovitz[27]	bimatoprost 0.003%	change from	20	21 days qd	qd (bid)	24.9	−2.6 (−3.6 bid)	−10% (−14% bid)
	bimatoprost 0.01%	baseline	20	followed by 7	qd (bid)	25.2	−5.7* (−5.7* bid)	−22% (−22% bid)
	bimatoprost 0.03%		20	days bid	qd (bid)	27.0†	−7.7* (−8.2* bid)	−28% (−30% bid)
	timolol 0.5%		20		bid	25.1	−3.6	−14%
	vehicle		20		bid	24.5	−0.5	−2%
Brandt[4]	bimatoprost 0.03%	change from	234	3 months	qd	24.2	−7.7*	−32%
	bimatoprost 0.03%	baseline	243		bid	23.9	−6.4*	−27%
	timolol 0.5%		119		bid	23.8	−5.4	−22%
Sherwood[40,c]	bimatoprost 0.03%	absolute	474	6 months	qd	24.2	−7.0*	−29%
	bimatoprost 0.03%	IOP	483		bid	24.1	−6.2	−26%
	timolol 0.5%		241		bid	23.9	−5.0	−21%
DuBiner[16]	bimatoprost 0.03%	change from	21	30 days	qd	24.3†	−7.0	−29%
	latanoprost 0.005%	baseline	22		qd	22.9	−5.5	−24%
	vehicle		21		qd	23.4	+0.7	+0%
Gandolfi[19,d]	bimatoprost 0.03%	absolute	119	3 months	qd	24.2	−6.9	−29%
	latanoprost 0.005%	IOP	113		qd	24.0	−6.4	−26%
Goldberg[20,e]	travoprost 0.0015%	absolute	190	9 months	qd	26.5	−8.0	−30%
	travoprost 0.004%	IOP	197		qd	26.4	−8.3*	−31%
	timolol 0.5%		185		bid	26.1	−7.1	−27%
Netland[33]	travoprost 0.0015%	absolute	202	12 months	qd	25.1	−6.5*	−26%
	travoprost 0.004%	IOP	197		qd	25.5	−6.9*	−27%
	latanoprost 0.005%		193		qd	25.7	−7.0*	−27%
	timolol 0.5%		195		bid	25.7	−5.5	−21%

bid = twice daily morning and evening; IOP = intraocular pressure; qd = once daily in the evening.

[a](bid) values in parentheses are from bid phase of the study. Drug was given once daily for 21 days then twice daily for 7 days.

[b]Change and percent change are calculated from the mean of all values at the last study visit versus baseline, except for the Laibowitz study[27] which was calculated from the values at day 21 of once-daily treatment and day 7 of twice-daily treatment. The percent change values are presented for comparison purposes. Statistics were not available for all studies therefore no differences are identified.

[c]This study is a meta-analysis using pooled data from the Brandt study[4] extended to 6 months and from a previously unpublished study.

[d]Midpoint of range used because mean was not presented.

[e]Baseline data obtained by personal communication with Author and is from intent-to-treat summary.

†Significantly ($p < 0.05$) higher baseline IOP compared with the other groups in this study.

*Significant ($p < 0.05$) difference from timolol.

At the end of the once-daily treatment phase, day 21, the mean IOP reduction from baseline was significantly greater in the bimatoprost 0.03% group than the timolol group at all time points except 8 AM. It should be noted that baseline IOP for the bimatoprost group was higher compared with the timolol group (27.0 vs 25.1 mm Hg, $p < 0.001$). The efficacy of any glaucoma medication is directly related to the baseline IOP.[21] For any IOP study, the group with the higher baseline IOP will more likely exhibit a larger change from baseline during treatment whereas the group with the lower baseline IOP will more likely show a lower absolute IOP during treatment. This effect is independent of the modality (eg. medication, laser procedure, filtering procedure) used to reduce IOP.

At the 8 AM measurement, the mean IOP decrease was not statistically different between once-daily versus twice-daily bimatoprost. This may have been from the relatively short duration of the study as a longer duration trial has shown that twice-daily bimatoprost use is less effective than once-daily.[4]

Adverse Events

No patient withdrew from the study prior to its completion date on day 28. Hyperemia was significantly higher in the bimatoprost 0.03% group than either the vehicle or timolol groups and was reported to be dose related. Mean hyperemia score ranges are reported in Table 2. No other side effects were reported in more than two patients during this short-term study.

3-Month Trial

Five hundred ninety-six (596) patients, with primary open angle glaucoma, ocular hypertension, chronic angle-closure glaucoma post iridotomy, exfoliation, glaucoma and pigmentary glaucoma, were enrolled in a 3-month study with a randomized blocks design, active control (timolol), and a 2:2:1 assignment ratio (bimatoprost 0.03%, once-daily, n = 234; bimatoprost 0.03%, twice-daily, n = 243; timolol 0.5%, twice-daily, n =119) (Table 1).[4] This assignment ratio denotes that for every 5 patients enrolled into the study, 2 will be assigned to the first category, 2 to the second, and 1 to the third. Hence, there will be twice as many patients in the experimental groups as the control group. In this study, the timolol group is the third category and is an active control group rather than a placebo control group. A study with 1:1:1 assignment would have three groups of equal numbers. All patients administered a drop of drug or vehicle to the cornea twice-daily between 7:00 and 9:00 AM and between 7:00 and 9:00 PM. Once-daily active drugs were given in the evening and a vehicle control was used in the morning. All bottles were masked. Post-washout IOPs were between 22 and 34 mm Hg. Diurnal IOP was measured at 8 AM, 10 AM, and 4 PM at all study sites and 8 PM at selected sites. The method for selecting the evening sites was not stated. The subset of evening measurements included 214 of 596 patients (36%). IOP measurements were performed at baseline, week 2, week 6, and month 3. Reduction from baseline IOP was the primary outcome measure. Statistical definitions of "noninferiority" and "superiority" were presented and used for analyses. A more traditional, and preferable, statistical approach would be to specify the type II or β error and choose an appropriate sample size.[18]

TABLE 2

Hyperemia Scores in Patients Treated with Bimatoprost, Timolol, or Vehicle for 21 or 28 Days[27]

Drug/Vehicle and Concentration	Study Length	Dose	Hyperemia Grade[a]
Bimatoprost 0.003%	21 days	once daily	0.65–0.78
Bimatoprost 0.01%	21 days	once daily	0.85–0.95*
	+7 days[b]	twice daily	0.93–1.00*
Bimatoprost 0.03%	21 days	once daily	0.80–0.98*
	+7 days[b]	twice daily	1.03–1.08*
Timolol 0.5%	28 days	twice daily	0.35–0.50
Vehicle	28 days	twice daily	0.50–0.6

*$p \leq 0.03$ vs timolol.

[a]Range of means of subjective grading (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, 3= severe).

[b]Indicates the last seven days of the study.

Single Time-Point Results

For every study visit at the 8 AM time point, the IOP reduction in both bimatoprost groups (once- and twice-daily) was significantly greater than in the timolol group.[4] Bimatoprost once-daily at 8 AM showed a greater IOP reduction than bimatoprost twice-daily at month 3 only ($p < 0.02$). The 8 PM measurement at the month 3 visit found the results of bimatoprost given once-daily not different from timolol. This may be due to a small sample size and inadequate statistical power. An estimate of power using variability (standard deviation, SD) from the baseline 8 PM time point and reported sample sizes (timolol = 45, bimatoprost = 83) was only 21% to detect a significant difference between groups with the reported 0.8 mm Hg mean difference. The sample size was large enough to have an 80% power to detect a 2 mm Hg difference in means.

Diurnal IOPs

Excluding the 8 PM measurements for lack of power noted above, compared with twice-daily timolol, once-daily bimatoprost reduced IOP significantly more at all time points. The average reduction was

1.7 mm Hg over the three time periods. Twice-daily bimatoprost reduced IOP an average of 0.8 mm Hg more than twice-daily timolol (also excluding the 8 PM data). This reduction was significant at 8 AM and 4 PM but not at 10 AM. Once-daily bimatoprost reduced IOP an average of 0.9 mm Hg more than twice-daily bimatoprost. This was statistically significant at 8 AM and 10 AM but not at 4 PM.

Adverse Events

Hyperemia, eyelash growth, pruritus, and ocular burning sensation were the only treatment-related adverse events with a greater than 5% frequency in any group (Table 3). "Mild" and "greater than mild" hyperemia were reported more in the bimatoprost groups (40% and 6%, respectively, for the once-daily group and 50% and 10%, respectively, for the twice-daily group) than the timolol group (8% and 2%, respectively, $p < 0.001$). Eyelash growth was significantly enhanced in both bimatoprost groups (26% once-daily and 34% twice-daily) compared with the timolol group (2%, $p < 0.001$). Ocular pruritus was reported more often in the twice-daily bimatoprost group than the timolol group (15% versus 3%, respectively, $p = 0.002$). Ocular burning sensation was significantly more prevalent for the timolol group than the bimatoprost once-daily group (9% vs 3%, respectively, $p = 0.02$).

6-Month Trial

This trial[40] is a pooled result from two independent studies. The 3-month reported study[4] was extended to 6 months and results were combined with a second study (unpublished). The study protocol, eligibility requirements, and randomization method (2:2:1) against timolol were the same as reported above[4] for both studies (Table 1). A total of 1,198 patients were included: bimatoprost 0.03% once-daily, n = 474 (234 + 240); bimatoprost 0.03% twice-daily, n = 483 (243 + 240); and timolol 0.5% twice-daily, n = 241 (119 + 122). Assigned drops were administered twice daily, 8:00 AM and 8:00 PM. A masked vehicle control was used in the morning for the once-daily bimatoprost group. Measurements were obtained at 8 AM, 10 AM, 4 PM, and 8 PM on baseline day, and months 0.5, 1.5, 3, and 6. Because of the pooled data, this study will be referred to as a meta-analysis. The primary outcome measure was diurnal IOP. This outcome measure differs from one of the component group's[4] outcome measure of change from baseline.

Mean diurnal IOP at 6 months ranged from 16.6 to 17.7 mm Hg for once-daily bimatoprost 0.03%, 17.0 to 18.7 for twice-daily bimatoprost 0.03%, and 18.4 to 19.3 for twice-daily timolol 0.5%. These differences reached statistical significance at every time point for once-daily bimatoprost versus timolol, and for all but at 10 AM for twice-daily bimatoprost versus timolol.

TABLE 3

Summary of Hyperemia Results from Five Clinical Trials of Patients Treated with Bimatoprost, Latanoprost, Timolol, or Travoprost for Varying Lengths of Time

Study	Drug and Concentration	Administration	Mild Hyperemia[a]	>Mild Hyperemia[a]
Brandt[4]	bimatoprost 0.03%	qd	40%*	6%*
	bimatoprost 0.03%	bid	50%*	10%*
	timolol 0.5%	bid	8%	2%
Sherwood[40]	bimatoprost 0.03%	qd	31%*	11%*
	bimatoprost 0.03%	bid	40%*	14%*
	timolol 0.5%	bid	8%	2%
Gandolfi[19,b]	bimatoprost 0.03%	qd	31%**†	5%**†
	latanoprost 0.005%	qd	12%**	2%**
Goldberg[20,c]	travoprost 0.0015%	qd	26%*	
	travoprost 0.004%	qd	32%*	
	timolol 0.05%	bid	7%	
Netland[33,c]	travoprost 0.0015%	qd	38%*	
	travoprost 0.004%	qd	50%*†	
	latanoprost 0.005%	qd	28%*	
	timolol 0.5%	bid	14%	

bid = twice daily morning and evening; qd = once daily in the evening.
[a]Values indicate % of patients exhibiting corresponding level of hyperemia.
[b]Results are for aggregate hyperemia and were not compared by grade.
[c]Did not report hyperemia by grade. Results are % of patients with clinically significant change from baseline.
*Significant difference from timolol group, $p < 0.001$
**Significant increase from baseline, $p \leq 0.001$
†Significant difference from latanoprost, $p < 0.001$.

Adverse Event

Conjunctival hyperemia was significantly elevated in the bimatoprost groups compared with the timolol group for gradings of "mild" (31%, once-daily bimatoprost; 40%, twice-daily bimatoprost; 8%, timolol, $p < 0.001$) and "greater than mild" (11%, once-daily bimatoprost; 14%, twice-daily bimatoprost; 2%, timolol, $p < 0.001$; Table 3). The authors proposed that some of the increase was due to baseline hyperemia, but it would be logical to assume that a change in hyperemia induced by treatment would be easier to demonstrate in eyes with less baseline hyperemia. Therefore, the differences in baseline hyperemia would favor detection of a drug-induced change more so in the timolol than the bimatoprost group. After accounting for baseline, there remained a significant percentage of patients with "more than a mild increase" in the bimatoprost groups compared with the timolol group (6% once-daily bimatoprost, 6% twice-daily bimatoprost, 0.4% timolol, $p = 0.002$). The percentage of patients in the bimatoprost groups who discontinued the study because of hyperemia, while low, was statistically greater than in the timolol group (3% once-daily bimatoprost versus 0.4% timolol, $p < 0.05$, and 5% twice-daily bimatoprost versus 0.4% timolol, $p < 0.01$). Eyelash growth also was noted more often in the bimatoprost groups than with the timolol group (36% once-daily bimatoprost, 48% twice-daily bimatoprost, 4% timolol, $p < 0.001$). Pruritus and eye dryness were statistically more prominent in the bimatoprost groups compared with the timolol group. Reports of a burning sensation were not statistically different between groups. Iris color changes were found in 1% of the patients in both bimatoprost groups and no patients in the timolol group. Seven of the 11 cases of iris color change were found at one investigational site. The protocol for determination of iris color change was not stated. Overall, 44 (9%) patients were discontinued from the once-daily bimatoprost group for any reason versus 18 (8%) from the timolol group (p = ns), and 85 (18%) from the twice-daily bimatoprost group ($p < 0.001$ versus timolol).

Summary of Studies of Bimatoprost Versus Timolol

The preponderance of evidence indicates that bimatoprost 0.03% once daily in the evening is more effective than timolol 0.5% twice daily at lowering IOP. Bimatoprost twice daily was usually more effective but at times equivalent to timolol. Results from diurnal analyses indicate that bimatoprost once daily was statistically more effective at lowering IOP than bimatoprost twice daily.

Adverse events such as hyperemia and pruritus appeared more often in the bimatoprost groups (once and twice-daily) than in the timolol groups. This finding occurred in every study and was statistically significant every time. Eyelash growth and iris color change were reported only in the bimatoprost groups.

BIMATOPROST VERSUS LATANOPROST

30-Day Trial

A randomized trial of patients with primary open-angle glaucoma or ocular hypertension (post-washout IOP between 23 and 34 mm Hg), compared bimatoprost 0.03% to latanoprost 0.005% or vehicle (Table 1).[16] One hundred-six (106) patients were enrolled into five treatment groups. Two groups, one receiving an undisclosed compound and another with an alternate formulation of bimatoprost, were not reported by the authors. The remaining three groups comprised bimatoprost once daily ($n = 21$), latanoprost once-daily ($n = 22$), and vehicle once-daily ($n = 21$). Intraocular pressure measurements were obtained at screening, baseline, day 14 and day 29. All drops were applied at 8 PM. Diurnal IOP measurements were obtained at 8 AM, 12 noon, 4 PM, and 8 PM on baseline day and day 29. Treatment was applied to both eyes and the patient response was recorded as the mean IOP of both eyes. The primary outcome measure was IOP change from baseline. Baseline diurnal IOPs were not equivalent for all groups (Table 1).

On day 14, significant reductions in IOP from baseline were reported for both bimatoprost and latanoprost ($p < 0.001$). Due to the significantly different baseline IOPs between groups, analysis of covariance (ANCOVA) was used to compare IOP reductions. No statistical differences were found in IOP reduction between bimatoprost and latanoprost.

On day 29, the mean reduction in IOP was similar for bimatoprost (7.0 mm Hg) and latanoprost (5.5 mm Hg, p = ns). The tendency for a greater IOP reduction in the bimatoprost versus latanoprost groups can be explained in part by the higher IOP at baseline in the bimatoprost group. As previously discussed, there is a direct correlation between baseline IOP and reduction in IOP with treatment.[21]

ANOVA was used for between-group comparisons of IOP area under the curve (AUC). The AUC analysis was intended as a measure of diurnal IOP control. A statistically significant difference was reported with bimatoprost showing a larger IOP lowering effect, 84 mm Hg·hour (mm Hg·hr) than latanoprost 64 mm Hg·hr ($p = 0.04$, 1-way ANOVA, pairwise t test).[16] The authors did not present the baseline AUC, which when calculated by the trapezoid method revealed an AUC of 292 mm Hg·hr for bimatoprost and 272 mm Hg·hr for latanoprost. This 20-point difference ($292 - 272 = 20$) in baseline AUC is identical to the post-drug 20-point difference ($84 - 64 = 20$). With identical pre- and post-treatment AUCs (20 mm Hg·hr) the data demonstrate equivalent diurnal control for both drugs.

A target IOP cumulative frequency histogram was presented that displayed the distribution of patients with IOPs at or below a given target IOP from ≤13 to ≤17 mm Hg. The authors reported a "higher percentage of patients in the bimatoprost group . . . achieved low target pressures."[16] However, less than 45% of the total data was included in this analysis. A comparison of the complete IOP data sets showed no significant differences between latanoprost and bimatoprost post-treatment groups.

Adverse Events

In this 30-day study, the publication did not report significant differences in adverse events, blood pressure, heart rate, or cup-to-disk ratio between any group including vehicle control.

3-Month Trial

A prospective, randomized trial of once-daily (evening) bimatoprost 0.03% or latanoprost 0.005% included 232 patients with primary open-angle glaucoma, ocular hypertension, chronic angle closure post iridotomy, and exfoliation and pigmentary glaucoma with post-washout IOPs between 22 and 34 mm Hg, randomized into two groups (bimatoprost = 119, latanoprost = 113) (Table 1).[19] IOP was measured at baseline, week 1, and months 1, 2, and 3. A 12-hour diurnal IOP at 8 AM, noon, 4 PM, and 8 PM was measured at baseline and 3 months. IOP was measured at 8 AM only at all other visits. Primary analyses included 8 AM IOP and percentage of patients at or below 17 mm Hg. Masked bottles were dispensed and compliance was estimated by query at each follow-up visit. The baseline grouping was notable for a statistically significant higher percentage of patients in the bimatoprost group who were not on any prior glaucoma medication (56% vs 42%, $p < 0.05$) and did not require washout.

Results 8 AM

Both drugs produced statistically significant decreases in IOP from baseline at all study time points ($p < 0.001$). Mean baseline IOP at 8 AM was reported as 25.7 mm Hg for both groups. No significant difference in mean IOP response was found between bimatoprost and latanoprost groups at 8 AM for any visit.

Diurnal Results

Diurnal IOP results comparing baseline and month 3 were not reported in aggregate. Mean diurnal baseline IOP was shown in graphic form and revealed skewed results at 12 noon and 4 PM with the average IOP in the bimatoprost group being numerically lower than in the latanoprost group. These baseline differences were reported as not statistically significant but the power was not stated. Statistically significant differences in post-drug mean IOP between the bimatoprost and latanoprost groups were reported for 12 noon and 4 PM, with no differences found at 8 AM and 8 PM. No comment was made regarding overall diurnal significance between groups, but with 2 of 4 time periods equivalent, no overall significance would be expected. Without overall significance, the point-by-point analysis becomes invalid, as post-hoc analyses are only valid to explore the source of established overall statistical significance.[6] In addition, the skewed results noted in the baseline data at these two time periods may be a source of baseline disturbance. A disturbing variable is one which has some nonrandom influence on the data.[14] In this case the baseline appears to be disturbing the post-drug results, that is, the 12 noon and 4 PM baselines show latanoprost numerically higher than bimatoprost in a similar way as the post-drug 12 noon and 4 PM results. As previously discussed, the drug with the lower pre-treatment IOP will more likely have a lower post-treatment IOP. When the baselines were numerically equal, as at 8 AM and 8 PM, the post-drug results were also equal. This indicates that a similar efficacy might have been found with adjustment for the baseline differences.

Analysis was made of the 12 noon diurnal time point. At this time only, a significantly greater percentage of patients in the bimatoprost group had IOPs reaching the ≤13 through ≤15 mm Hg levels compared with the latanoprost group. A diurnal mean pressure response histogram of all time points throughout the day, including all IOPs, would have provided more complete information with less chance of statistical aberrancy. This analysis was based on approximately 50% of the 12 noon data. It was noted that this study analyzed absolute IOP while other bimatoprost studies analyzed change in IOP.[4,16,27]

It can be concluded that bimatoprost 0.03% once-daily lowered IOP as effectively as latanoprost 0.005% once-daily. Statements of greater IOP efficacy with bimatoprost were based on analyses using incomplete data sets, and not accounting for differences in baseline IOP.

Adverse Events

Few patients in each group discontinued the study for reasons of tolerability, 6 of 119 (5%) in the bimatoprost group and 5 of 113 (4%) in the latanoprost group (p = ns). Conjunctival hyperemia (36% for bimatoprost vs 14% for latanoprost, $p \leq 0.001$) and eyelash growth (13% for bimatoprost vs 4% for latanoprost, $p < 0.03$) were more common in the bimatoprost group, whereas headache was more com-

mon in the latanoprost group (4% for latanoprost vs 0% for bimatoprost, $p < 0.03$) (Table 3). No other important adverse effects such as cystoid macular edema or uveitis were noted for either group.

Summary of Studies of Bimatoprost Versus Latanoprost

The two studies to date[16,19] demonstrated equivalence of bimatoprost 0.03% and latanoprost 0.005% with regard to lowering IOP. Both drugs effectively reduced IOP from the study baselines.

The 3-month study[19] demonstrated statistically significant increases in side effects such as hyperemia and eyelash growth for bimatoprost compared with latanoprost. Prevalence of headache, while low, was significantly greater in the latanoprost group in one study.[19]

Overall, it can be concluded that bimatoprost used once per evening was more effective than timolol and as effective as latanoprost at lowering IOP, but with a higher percentage of side effects with bimatoprost compared with either timolol or latanoprost.

Travoprost

Travoprost (AL-6221), a PGF2a analog, is an isopropyl ester of the (+) enantiomer of fluprostenol. Chemically it has the name isopropyl (Z)-7-[1R,2R, 3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α-tri fluoro-m-tolyl) oxy]-1-butenyl) cyclopentyl]-5-heptenoate. It is structurally similar to other prostaglandin F2a analogs such as latanoprost (Fig. 1).22,23 It is the isopropyl ester of the more active enantiomer of fluprostenol, a selective FP prostanoid receptor agonist.13, 17,22,23

OCULAR HYPOTENSIVE MECHANISM OF ACTION

There is no clinical study of the mechanism of action by which travoprost reduces IOP. In a recent animal study,[46] aqueous humor dynamics were studied in monkeys with unilateral laser-induced ocular hypertension before and after bilateral travoprost 0.004% administration. Treatment was twice daily for 2 days and on the morning of the third day. IOP was measured by pneumatonometry. Aqueous flow and outflow facility were determined by a fluorophotometric method. Uveoscleral outflow was calculated. In the hypertensive eyes on the treatment day versus baseline day, IOP was significantly reduced by 7.7 mm Hg at 2.5 hours and by 9.1 mm Hg at 16 hours after treatment ($p = 0.02$). Travoprost increased uveoscleral outflow in the normotensive eyes, but not in the hypertensive eyes. Statistical power was limited by the small sample size and large standard deviations. There was no reported drug effect on aqueous flow and outflow facility in either eye. These results are consistent with those of other topical prostaglandin $F_{2\alpha}$ analogs and prodrugs.[3,5,10,26,31,38,43,44,47,52]

TRAVOPROST VERSUS TIMOLOL

9-Month Trial

A randomized, prospective, active-control (timolol), parallel group study included 573 patients with open-angle, exfoliation, pigmentary glaucoma, or ocular hypertension in a 1:1:1 design (Table 1).[20] Groups included: travoprost 0.0015%, once daily, n = 190; travoprost 0.004%, once daily, n = 197; and timolol 0.5%, twice daily, n = 185. Inclusion IOPs were between 24 and 36 mm Hg at 9 AM and 21–36 mm Hg in the same eye at 11 AM and 4 PM. Drops were instilled at 9 AM and 9 PM. A vehicle control was given to those in the travoprost groups for morning use while the timolol group used active drug twice daily. Measurements were obtained at three pre-randomization visits (screening plus 2 baseline), and months 0.5, 1.5, 3, 4.5, 6, and 9. Diurnal measurements (9 AM, 11 AM, 4 PM) were obtained at both baselines, and months 0.5, 3, and 9. Measurements were obtained at 9 and 11 AM only at months 1.5, 4.5 and 6. Three data sets were analyzed: safety, intent-to-treat, and per protocol. Analysis of safety included all 573 patients. Intent-to-treat included 572 patients and per protocol included 507 patients. Primary outcome measure was the mean IOP. It was not stated if this outcome was for a single time period or the average diurnal pressure. Iris pigmentation was judged by independent readers at the Alcon Reading Center using iris photographs from baseline and all visits from month 1.5 to study end.

Results

Travoprost 0.004% lowered IOP more than timolol in 11 of 15 measurement points, from 0.7 to 1.4 mm Hg. Change from baseline demonstrated a 30–33% decrease for travoprost compared with a 25–29% decrease for timolol.

Adverse Events

Ocular hyperemia was the most frequent adverse event, being reported in 64 of 197 (32%) patients in the travoprost 0.004% group versus 13 of 186 (7%) in the timolol group ($p < 0.0001$) (Table 3). Iris pigmentation was noted in 4% of the travoprost group and none in the timolol group. Eyelash changes were found in 150 of 197 patients (76%) in the travoprost group compared with 6 of 186 (3%) receiving timolol. Ocular stinging and burning was reported infrequently, but was significantly higher in the travoprost versus timolol group (7% vs 2%, $p = 0.03$), as was pruritus (7% vs 2%, $p = 0.03$).

TRAVOPROST VERSUS TIMOLOL AND LATANOPROST

12-Month Trial

A randomized, prospective, active-control (timolol), parallel group study included 801 patients with open-angle, exfoliation, pigmentary glaucoma or ocular hypertension in a four group 1:1:1:1 design (Table 1).[33] Groups included the following: travoprost 0.0015%, once-daily, n = 205; travoprost 0.004%, once-daily, n = 200; latanoprost 0.005%, once-daily, n = 196; and timolol 0.5%, twice-daily, n = 200. Baseline IOPs were between 24 and 34 mm Hg inclusive at 8 AM and 21 to 36 mm Hg at 10 AM and 4 PM. Drops were applied at 8 AM and 8 PM. For both the travoprost group and the latanoprost group, a vehicle was used in the morning. Timolol active drug was used twice-daily. All bottles were masked. Measurements were obtained at baseline and 0.5, 1.5, 3, 4.5, 6, 9, and 12 months. Diurnal measurements (8 AM, 10 AM, 4 PM) were obtained at baseline, 0.5, 3, 6 and 12 months. At months 1.5, 4.5 and 9, measurements were at 8 and 10 AM only. Three data sets were analyzed: safety, intent-to-treat, and per protocol. Analysis of safety included all 801 patients. Intent-to-treat included 787 patients and per protocol included 760 patients. Primary outcome measure was the mean IOP at 8 AM, 10 AM, and 4 PM. Iris color changes were measured using color iris photographs read by four ophthalmologists who were masked and had not examined the patients.

Travoprost Versus Timolol

Mean baseline IOPs for travoprost 0.004% and timolol were 25.5 mm Hg and 25.7 mm Hg, respectively. Compared with baseline, travoprost and timolol significantly reduced IOP by 7.1 mm Hg (28%) and 5.9 mm Hg (23%), respectively. At every study time point, the IOP reduction was greater for travoprost than for timolol. Combining the 18 study measurements, the average difference in IOP between timolol and travoprost was 1.4 mm Hg. It can be concluded that travoprost 0.004% was more effective at lowering IOP than timolol.

Travoprost Versus Latanoprost

From an average baseline IOP of 25.5 and 25.7 mm Hg for travoprost and latanoprost, respectively, mean IOP was reduced to the range of 17.5 to 19.7 mm Hg for travoprost and 17.9 to 19.5 mm Hg for latanoprost. This equates to an average decrease from baseline of 7.1 mm Hg (28%) and 7.0 mm Hg, (27%), respectively (p = ns). The overall results demonstrated that travoprost 0.004% lowered IOP equally as well as latanoprost 0.005%. The authors reported a small, statistically greater, IOP decrease in the travoprost group compared with the latanoprost group at the 4 PM measurement. In the absence of overall statistical significance, this subset analysis is unwarranted.[6,9]

Travoprost and Special Response to Race

Comparisons in a subset of black patients treated with travoprost (n = 49) versus latanoprost (n = 43) found significantly lower post-treatment pooled IOPs in the travoprost group at each time point. A pooled IOP is the average IOP of all visits at each time point. On average, baseline IOP was 1.0 mm Hg lower in the travoprost black patient subgroup compared with the latanoprost black patient subgroup (Fig. 2, note 4 PM baseline).[8] This unequal starting point, statistically significant at 4 PM, creates a data disturbance that may account for the results. The impact of unequal baselines and adjustments required for disturbing variables were discussed previously.

Adverse Events

Clinically significant changes in hyperemia were reported in 99 of 200 patients (50%) in the travoprost group, 54 of 196 patients (28%) in the latanoprost group, and 28 of 200 patients (14%) in the timolol group (Table 3). Statistical analysis of these differences was not presented by the authors.[8] Chi-square analysis found that the 50% prevalence of hyperemia in the travoprost group was significantly ($p < 0.0001$) greater than the 28% in the latanoprost

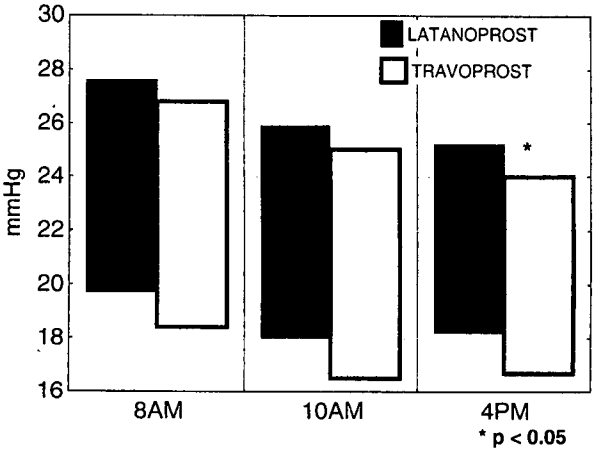

Fig. 2. In the Netland study,[33] analysis was made of a subgroup of black patients treated for 12 months with once-daily latanoprost 0.005% (n = 43; filled bars) or once-daily travoprost 0.004% (n = 49; open bars). The top of the bars represent the mean baseline IOP at each time point. The bottom of the bars represent the mean treatment IOP at each time point. The vertical height is the change in IOP in mm Hg from baseline to treatment at each time point, respectively. Baseline IOPs were lower for the travoprost group compared with the latanoprost group at all time points, reaching statistical significance at 4 PM. Data from Table 3 of Netland.[33] (*$p < 0.05$ comparing latanoprost vs travoprost IOPs on baseline day.)

group and the 14% in the timolol group. Additionally, the latanoprost group demonstrated a significantly greater increase in hyperemia compared with the timolol group (28% vs 14%, $p < 0.001$, Table 3).

Iris pigmentation changes were similar in the travoprost and latanoprost groups (3% vs 5%, p = ns). Eyelash changes were noted in 112 of 196 (57%) patients in the travoprost group versus 50 of 194 (26%) patients in the latanoprost group ($p < 0.0001$). Travoprost and latanoprost had a small but significantly higher prevalence of reports of pruritus compared with timolol (8% travoprost, 6% latanoprost, 2% timolol, $p < 0.05$). No other important differences were reported.

Summary

Travoprost 0.004% once-daily decreases IOP more than timolol 0.5% twice-daily but with a higher occurrence of ocular adverse effects such as hyperemia, lash changes, and pruritus.

Travoprost 0.004% once-daily and latanoprost 0.005% once-daily were equally effective at lowering IOP in all patient groups including the black patient subset. The only meaningful differences were the significantly greater prevalence of hyperemia and lash growth in the travoprost 0.004% group compared with the latanoprost or timolol groups.

Conclusions

In this review, we have examined the most recent literature available for bimatoprost and travoprost used alone to lower IOP. In each case, the results support the conclusions that these agents, used once-daily, were more effective than timolol used twice-daily and as effective as latanoprost used once-daily in terms of the ability to reduce IOP. Latanoprost has demonstrated greater efficacy than timolol in lowering IOP in prior publications.[1,2,11,12,21,32,51]

Bimatoprost demonstrated significant increases in both frequency and severity of hyperemia and eyelash growth compared with timolol or latanoprost. Similar increases occurred with travoprost compared with timolol or latanoprost. Compared with timolol, latanoprost produces eyelash changes and mild conjunctival hyperemia.[1,2,11,12,21,24,32,48] Bimatoprost, travoprost, and latanoprost produce iris color darkening at a similar frequency.

Method of Literature Search

The National Library of Medicine database was searched using the PubMed engine (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). All available years were included. No foreign language articles were found. Keywords used in the search: *travoprost, Travatan, bimatoprost, Lumigan.*

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CLINICAL STUDY REPORT

A Multicenter, Double-masked, Randomized Study to Evaluate the Safety and Efficacy of Twice-daily 0.01% Bimatoprost / 0.15% Brimonidine Tartrate / 0.5% Timolol Ophthalmic Solution (Triple Combination) Compared With Twice-daily COMBIGAN® in Patients Who Have Primary Open-angle Glaucoma or Ocular Hypertension

Study Number:	192024-063
Phase:	3
Name of Investigational Product:	0.01% Bimatoprost / 0.15% Brimonidine Tartrate / 0.5% Timolol ophthalmic solution
Brief Description:	Multicenter, Double-masked, Randomized, Phase 3 Study
Study Initiation Date (First Patient Enrolled):	28 June 2011
Study Completion Date (Last Patient Completed):	25 September 2013
Coordinating Investigator:	Dr. Curt Hartleben-Matkin, Fundación de Asistencia Privada "Conde de Valenciana," Distrito Federal, México
Allergan Responsible Medical Officer:	Susan Schneider, MD Vice President Ophthalmology Therapeutic Area Head Glaucoma and wAMD Allergan – Global Drug Development
Sponsor:	Allergan Produtos Farmacêuticos Ltda. 1955 Cardoso de Melo Avenue, 13th Floor São Paulo, SP - 04548-005 - Brazil Phone: +55 11 3048-0500 Fax: +55 11 3849-4575 Allergan S.A. de C.V. 505 Santa Fé Avenue. 11th Floor. Del. Cuajimalpa. México, D.F. – 05349 – México Phone: +52 55 5999-8500 Fax: +52 55 5682-6987

This study was conducted in compliance with Good Clinical Practice.

Name of Finished Product: TRIPLE COMBINATION

Name of Active Ingredient: Bimatoprost 0.01% / brimonidine tartrate 0.15% / timolol 0.5% ophthalmic solution

Number and Title of Study: 192024-063: A Multicenter, Double-masked, Randomized Study to Evaluate the Safety and Efficacy of Twice-daily 0.01% Bimatoprost / 0.15% Brimonidine Tartrate / 0.5% Timolol Ophthalmic Solution (Triple Combination) Compared With Twice-daily COMBIGAN® in Patients Who Have Primary Open-angle Glaucoma or Ocular Hypertension

Investigators: In México, the principal investigators were José Antonio Paczka Zapata, Curt Hartleben-Matkin, Alfonso García López, Félix Gil Carrasco, Jorge Eugenio Valdez García, and Gustavo Velasco Gallegos. In Colombia, the principal investigators were María Fernanda Delgado Morales and Juan Camilo Parra Restrepo.

Study Centers: A total of 8 centers, 6 in México and 2 in Colombia, participated in the study.

Study Period:
Study Initiation Date (First Patient Enrolled): 28 June 2011
Study Completion Date (Last Patient Completed): 25 September 2013

Phase of Development: 3

Publication(s): None

Objectives: To evaluate the efficacy and safety of 0.01% bimatoprost / 0.15% brimonidine tartrate / 0.5% timolol ophthalmic solution (hereafter referred to as TRIPLE COMBINATION) twice-daily compared with COMBIGAN (0.2% brimonidine tartrate / 0.5% timolol ophthalmic solution) twice-daily administered for 12 weeks in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT)

Methodology: This was a 12-week, multicenter, double-masked, randomized, active controlled, parallel study comparing twice-daily bilateral administration of TRIPLE COMBINATION with COMBIGAN in patients with POAG or OHT.

Number of Patients (Planned and Enrolled):
Planned: Approximately 184 patients were planned to be enrolled.
Enrolled: A total of 192 patients were enrolled in the study and 175 patients completed the study.

Diagnosis and Main Criteria for Eligibility:
Diagnosis: Patients with OHT or POAG requiring bilateral intraocular pressure (IOP)-lowering treatment.

Test Product, Dose and Mode of Administration, Batch Number: 0.01% bimatoprost / 0.15% brimonidine tartrate / 0.5% timolol ophthalmic solution (TRIPLE COMBINATION) twice-daily in both eyes for 12 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: COMBIGAN ophthalmic solution twice-daily in both eyes for 12 weeks.

Duration of Treatment: 12 weeks

Statistical Methods:

Three analysis populations were defined: safety, modified intent-to-treat (mITT), and per protocol (PP).

Categorical variables were summarized by frequency count (n) and percentages (%). Continuous variables were summarized by mean, standard deviation (SD), median, minimum, and maximum.

Worse eye was defined as the eye with greater hour 0 IOP at baseline (day 0).

The primary efficacy variable was the mean worse eye IOP change from baseline (hereafter referred to as mean IOP change from baseline) at week 12 in the mITT population. The comparison between TRIPLE COMBINATION and COMBIGAN was assessed by testing the null hypothesis (H_o) versus the alternative hypothesis (H_a). H_o was that there was no difference in mean IOP change from baseline (day 0) at week 12 for patients treated with TRIPLE COMBINATION compared to patients treated with COMBIGAN. H_a was that there was a difference in the mean IOP change from baseline at week 12 for patients treated with the TRIPLE COMBINATION compared to patients treated with COMBIGAN. This hypothesis was tested using the 2-sample t-test.

The secondary efficacy variables were the mean worse eye IOP (hereafter referred to as mean IOP) and the mean IOP change from baseline at weeks 1, 2, 4, 8, and 12. These analyses were evaluated using the mixed-model repeated measure (MMRM) analysis in which the model had terms for treatment, country, systemic beta-adrenergic blocking agents use (yes/no), time, and a treatment by time interaction term.

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The method used for the primary efficacy analyses was repeated for mean IOP and mean IOP change from baseline for all postbaseline visits. This was also repeated in a subpopulation of patients with baseline mean IOP $\geq$ 25 and < 25 mm Hg.

Summary of Results:

Overall, 192 patients were enrolled in this study. A total of 190 patients were included in the mITT population and 191 in the safety population; 175/190 (92.1%) patients included in the mITT population completed the study as planned. The TRIPLE COMBINATION group included 93 patients in the mITT population with 7/93 (7.5%) discontinued: 5 due to adverse events (5/93 [5.4%]); 1 lost to follow-up (1/93 [1.1%]); and 1 discontinued due to personal reasons (1/93 [1.1%]). The COMBIGAN group included 97 patients in the mITT population with 8/97 (8/2%) prematurely discontinued: 4 due to adverse events (4/97 [4.1%]) and 4 lost to follow-up (4/97 [4.1%]).

The mean age of the patients was 59.4 years, with the majority of patients $\leq$ 65years (140/190 [73.7%]). The majority of the patients were female (149/190 [78.4%]). All patients in the mITT population (190/190 [100%]) were self-reported as Hispanic. The mean height was 158.7 cm and the mean weight was 70.8 kg. The majority of patients had brown irides (133/190 [70.0%]). The 2 treatment groups were comparable with respect to demographic and baseline characteristics.

Efficacy:

- The primary efficacy analyses demonstrated the statistical superiority of TRIPLE COMBINATION over COMBIGAN. At week 12, TRIPLE COMBINATION provided -0.85 mm Hg (p = 0.028) greater mean IOP change from baseline compared to COMBIGAN in the mITT population.
- Statistical superiority of TRIPLE COMBINATION over COMBIGAN was also observed at all other study visits. At weeks 1, 2, 4, and 8, TRIPLE COMBINATION provided greater mean IOP change from baseline compared to COMBIGAN (week 1: -1.28 mm Hg [p = 0.006]; week 2: -1.40 mm Hg [p = 0.001]; week 4: -0.92 mm Hg [p = 0.019]; week 8: -0.85 mm Hg [p = 0.047]) in the mITT population.

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- In a subpopulation of patients with baseline mean IOP $\geq$ 25 mm Hg, TRIPLE COMBINATION achieved a mean IOP change from baseline that was both statistically and clinically significantly superior to that of COMBIGAN at week 12 in both the mITT and PP populations (-1.96 mm Hg [p = 0.002] and -1.35 mm Hg [p = 0.032], respectively).

Safety:

- The vast majority of adverse events were ocular in nature. Of these, only conjunctival hyperaemia, eye irritation, and dry eye were statistically significantly greater in the TRIPLE COMBINATION group than the COMBIGAN group ($p \leq 0.016$). These were also the most frequently reported treatment-related adverse events and were mostly reported as mild in severity. These adverse events resulted in only 5 discontinued patients (conjunctival hyperaemia [3/93 (3.2%)] and eye irritation [2/93 (2.2%)]) in the TRIPLE COMBINATION group.
- Four serious adverse events were reported in 3 patients (3/191 [1.6%]). None were ocular. All 3 patients with serious adverse events were in the TRIPLE COMBINATION group. None of these serious adverse events were considered treatment-related, and there were no deaths reported during the study period.

Conclusion:

TRIPLE COMBINATION provides a clinically meaningful and statistically significantly greater IOP-lowering effect than COMBIGAN, and has an acceptable safety and tolerability profile in patients with primary open-angle glaucoma or ocular hypertension with elevated IOP.