Original Research Article

Comparison of Preserved Bimatoprost 0.01% with Preservative-Free Tafluprost: A Randomised, Investigator-Masked, 3-Month Crossover, Multicentre Trial, SPORT II

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ABSTRACT

Importance: This study compares the efficacy and tolerability of a preservative-free prostaglandin analogue (tafluprost 15 mg/ml) to a prostaglandin analogue that uses 0.02% of benzalkonium chloride (bimatoprost 0.1 mg/ml).

Background: Different prostaglandin analogues have been commercially approved, with differences in tolerability.

Design: Prospective, randomised, investigator-masked, 3-month crossover, multicentre trial.

Participants: Sixty-four patients with ocular hypertension or open-angle glaucoma were randomised to two groups, after a 4-week washout period from their current topical drop regimen.

Methods: Participants were randomised to tafluprost (Group 1; n=33) or bimatoprost (Group 2; n=31). At month 3, each group switched to the opposite treatment. IOP was evaluated at multiple timepoints.

Main Outcome Measures: The primary outcome was difference in mean IOP between the two groups at the final visit. Secondary outcomes included change from baseline IOP at month 3 and month 6, difference in mean IOP at month 3, and difference in IOP at all timepoints. Safety outcomes included best-corrected visual acuity (BCVA), adverse events, ocular tolerability, optic nerve assessment, and slit lamp biomicroscopy.

Results: Both medications significantly lowered IOP at month 6 compared to baseline: 5.4 mmHg (27%) for tafluprost and 6.8 mmHg (33%) for bimatoprost ($p < 0.0001$). No significant differences in any of the safety measures (including conjunctival hyperemia) were detected.

Conclusions and Relevance: Bimatoprost produced a statistically significant greater IOP reduction compared to tafluprost with minimal to no difference in side effects. This should be borne in mind when weighing up the pros and cons of preserved versus preservative-free prostaglandin analogue therapy. (ClinicalTrials.gov Identifier: NCT02471105)

Keywords: Prostaglandin, preservative-free, tafluprost, bimatoprost, crossover

1. INTRODUCTION

By 2040, more than 111 million people globally are expected to have glaucoma; the damage from the disease to the optical nerve from elevated intraocular pressure (IOP) will eventually lead to blindness if not properly treated.[1,2] In today's clinical settings, controlling and stablising IOP is the sole means to prevent progression of the disease. [3-5] It is a well-known and well-reported fact that the risk of glaucoma progression decreases by as little as 10% to as much as 19% for each mmHg reduction in IOP.[4,6-9]

Topical prostaglandin analogue (PGA) monotherapy eyedrops are most frequently used as first choice due to the safety, efficacy, convenience, and cost-effectiveness of the drug class.[7,10-12] Non-compliance among patients remains high but studies have shown this can be offset by once-daily dosing.[12]

Several different PGAs have been commercially approved worldwide, with key differences in tolerability, which is related to the active compound and use of preservatives and/or excipients.[13-20] It is well accepted that preservatives can damage the ocular surface and lead to adverse events (AEs) such as local toxicity, allergic reactions, and ocular surface disease.[21-26] Preservative-free PGAs have been introduced to overcome those issues.

One systematic review of 32 randomised clinical trials found bimatoprost reduced IOP more than other PGAs, but latanoprost was the best tolerated.[27] The SPORT I trial compared the safety and efficacy of preservative-free latanoprost to preservative-free bimatoprost and found preservative-free bimatoprost had a superior efficacy over preservative-free latanoprost, with a statistically significant difference in hyperemia scores that favored latanoprost.[13]

This current study, SPORT II, investigated the efficacy, safety, and tolerability of preserved bimatoprost with preservative-free tafluprost in patients with open-angle glaucoma who were already being treated with a PGA.

2. METHODS

SPORT II was a prospective, randomised, investigator-masked, crossover clinical study carried out at six centres in Europe, and was designed to be a subsequent clinical trial to SPORT I.[13] As such, the methodology was almost identical. SPORT II was approved by local ethics committees in agreement with the tenants of the Helsinki declaration and its amendment of October 2000 (Edinburgh, UK). Informed

consent was obtained from all patients and the study was registered with the EudraCT (number 2014-004442-10) and clinicaltrial.gov (number NCT02471105). As in SPORT I, patients who fulfilled the eligibility criteria listed below, who were able and willing to participate in the study for the whole duration of the follow up, and who were willing to sign the consent form were included in the study.

Study population

Inclusion criteria
Patients with ocular hypertension, exfoliation glaucoma, or primary open-angle glaucoma that required bilateral treatment, that were at least 18 years of age and willing to participate in the study for its duration and follow-up, and able to understand and willing to sign the consent form.

Exclusion criteria
Subjects were excluded if they: were unwilling to sign informed consent; younger than 18 years old; had an ocular condition that was a safety concern or could interfere with the study results; had a visual field defect with an mean defect value above -15dB on either eye on Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) or Octopus (Haag-Streit AG, Koeniz-Berne, Switzerland) and/or threatening fixation; wore contacts; had closed/barely open anterior chamber angles or history of acute angle closure on either eye as assessed by gonioscopy; had ocular surgery (other than glaucoma surgery) or argon laser trabeculoplasty within the previous 3 months before study enrollment; had glaucoma surgery within the previous 6 months on either eye before study enrollment; had ocular inflammation/infection occurring within the previous 3 months before the pretrial visit on either eye; were on concomitant topical ocular medication that could interfere with study medication on either eye; had known hypersensitivity to any component of the trial drug solutions; had a history of refractive surgery; were pregnant; had an inability to adhere to treatment/visit plan; or had participated in any other interventional clinical trial (i.e., requiring informed consent) involving an investigational drug within 1 month before the pretrial visit.

Withdrawal
Subjects would be withdrawn from the study if they became pregnant or if, in the opinion of the investigator, it was medically necessary, or if the patient withdrew consent. Subjects who failed to return for follow-up visits were also withdrawn.

Study Design

Figure 1 describes the study design, which differs from SPORT I only in the PGAs being studied.[13] To briefly recap: Enrolled patients who were on topical therapy at the screening visit underwent a washout period of 4 weeks before the baseline visit. To avoid exposing the patient to any additional risks of a second washout, the patients were switched from the first to the second therapy without additional washout (see Figure 1.)

After the screening visit (and after washout period for treated patients), the study subjects were scheduled to undergo a baseline visit IOP assessment, and then were randomised to receive either bimatoprost or tafluprost once in the evening. At month 3, patients were switched to the opposite treatment regimen.

Subjects had a final evaluation of IOP levels, safety, and tolerability after the second three months (6 months from baseline). Intermediate safety visits were scheduled at the discretion of the investigator.

Sample Size Calculation

The sample size calculation is based on the assumption that a difference in mean IOP of 1 mmHg between the 2 treatment groups is clinically relevant. About 60 patients are needed in the cross-over, given a type I error of 0.05 and a statistical power of 80%, with a standard deviation of 2.8 mmHg. Assuming approximately 10% rate of withdrawals, 67 patients had to be included and randomized.

Clinical assessments

IOP measurements

Two consecutive IOP measurements, using Goldmann tonometry, were taken. If these two measurements differed by more than 1 mmHg, a third measurement was made, and the mean of all three measurements was recorded. IOP measurements were taken at 08:30; 12:30 and 16:30 ± 1 hour at all visits. For the analysis, the average of the three diurnal measurements was considered. Both the investigator and the reader were masked.

Visual field measurements

Visual field measurements were performed using the Humphrey or Octopus perimeter at baseline and at exit visit.

Visual acuity and refraction

Best-corrected Snellen visual acuity (BCVA) was evaluated at screening and baseline, and at months 3 and 6. Clinically relevant decreases in BCVA from the pretrial visit were reported as an AE.

Lid and slit lamp examination (biomicroscopy)
Lid and slit lamp examinations of subjects' skin and margins of upper and lower lids were performed at all visits. Deposition of pigment on the corneal endothelial layer or the lens capsule or any abnormalities of the lids, conjunctiva (palpebrae and bulbi), cornea, anterior chamber, iris and lens were graded as mild, moderate or severe. Conjunctival hyperemia was scored using the previously published scoring chart for hyperemia.[28] Punctate epitheliopathy was scored using the Oxford scale.[29] Aphakia or pseudophakia (with specification of implant lens position) was reported. Cells present in a slit of 2 mm were graded as mild (3 to 5 cells), moderate (6 to 20 cells), or severe (>20 cells).

Ophthalmoscopy
Ophthalmoscopy to assess the status of the optic nerve head was performed at screening and at all visits. The vertical cup/disc ratio was scored and the presence of optic disc hemorrhages was recorded.

Safety
In addition to optic nerve head assessments and slit lamp biomicroscopy, other safety outcomes included BCVA, adverse events, and ocular tolerability of the topical medications.

Study outcomes
Primary outcomes
The primary outcome was the difference in mean diurnal IOP values (an average of three measurements) between the two groups at month 6.

Secondary outcomes
Secondary outcomes included the between-group differences in IOP from baseline IOP to month 3 and month 6, respectively. Other secondary outcomes included the between-group difference in mean IOP from screening visit to month 3 and month 6; and the between-group difference in IOP at month 3.

Statistical analyses
If both eyes were eligible, only the worse eye (defined as the eye with highest baseline IOP) was used for analytical purposes.

Data was analyzed using linear mixed models with random effects to account for repeated measurements on the same subjects (multiple time-points). Both analysis per period and per medication were performed. The effect of carryover in the cross-over design was tested with an interaction term between the period and the medication. To test the proportional changes of IOP from baseline, we used a generalised linear model with a Gamma distribution for the error and log link function. All statistical analyses have been conducted in R (R Foundation for statistical computing) by a statistician masked to the treatment.

3. RESULTS

Demographics

A total of 69 subjects were recruited; one patient failed screening and two others left the study before randomization. Therefore, 66 subjects (30 male; 36 female) were randomised; of these one subject was excluded because there were no measurements beyond screening and baseline, one subject did not have screening or baseline measurements, and one subject was missing the month 3 visit, leaving 64 subjects randomised to either Group 1 (n=33), which received tafluprost in the first time period or Group 2 (n=31), which received bimatoprost in the first time period.

The mean age at baseline was 70.1 ± 8.3 years. The visual field defect mean deviation at baseline was -0.59 ± 4.33 dB. The cup-to-disc ratio at baseline was 0.55 ± 0.22. No significant differences in baseline conditions could be detected between the two arms. As noted earlier, the majority of subjects (95%) had prior topical medication use (see Table 1).

Prior Medication	**Group 1 (n=33)**	**Group 2 (n=31)**
Prostaglandins	26 (78%)	25 (81%)
Bimatoprost	15 (45%)	15 (49%)
Latanoprost	9 (27%)	6 (19%)
Travoprost	1 (3%)	3 (10%)
Tafluprost	1 (3%)	1 (3%)
Prostaglandin + timolol	*3 (9%)*	*1 (3%)*
Timolol only	5 (16%)	4 (13%)
Brinzolamide	1 (3%)	0 (0%)
Treatment-naive	1 (3%)	2 (6%)

Table 1. Prior medication use. P-values were all calculated with chi-squared test for contingency tables.

Efficacy

No significant differences were found between the two groups at screening or baseline. Group 1 had a higher IOP than Group 2 at month 3, but this difference was not statistically significant (p = 0.06). At month 6, however, Group 1 (bimatoprost after tafluprost) had a statistically significantly lower IOP than Group 2 (tafluprost after bimatoprost; p = 0.03). A carryover effect was not evident, as the mean estimates after the crossover switch were very similar for the same medication regardless of group assignment (see Table 2 and Figure 2). The random effect to account for clustering by centres was significant (p = 0.003), indicating notable variations among study sites. Although the 95% CI for the estimates of Group 1 and Group 2 partially overlapped at 6 months, the 95% CI for the difference did not include 0 (i.e., the test was significant at 0.05) (see Table 2 and Figure 2).

	Screening	**Baseline**	**3 Months**	**6 Months**
Group 1				
IOP	15.2	20.3	14.7	13.3
(95% CI), mmHg	(13.5, 16.9)	(18.6, 22.0)	(13.0, 16.4)	(11.6, 15.1)
difference in IOP from baseline	-5.0		5.5	6.9
(95% CI), mmHg	(-5.8, -4.3)		4.8, 6.3)	(6.2, 7.7)
difference in IOP from screening		5.0	0.5	1.9
(95% CI), mmHg		(4.3, 5.8)	(-0.2, 1.2)	(1.1, 2.6)
Group 2				
IOP				
(95% CI), mmHg	15.7	20.0	13.5	14.8
difference in IOP from baseline	(14.0, 17.4)	(18.3, 21.7)	(11.7, 15.2)	(13.1, 16.5)
(95% CI), mmHg	-4.3		6.6	5.2
difference in IOP from screening	(-5.1, -3.6)		(5.8, 7.3)	(4.5, 6.0)
(95% CI), mmHg		-4.3	2.2	0.9
		(-5.1, -3.6)	(1.5, 3.0)	(0.2, 1.6)
between-group difference in IOP				
(95% CI), mmHg	-0.5	0.3	1.3	-1.5
	(-1.7, 0.8)	(-1.0, 1.5)	(0.0, 2.5)	(-2.7, -0.2)

Table 2. Mean IOP and difference in mean IOP at different timepoints.

Analysis by medications

Analysis of the overall differences in the two medications was done by using the same mixed model as the one to discern between-group differences, but using the treatment and the group as predictors. The interaction between the treatment and the Group was used to test whether the group sequence could influence the effect of either medication (to indicate a significant carryover effect). No significant effect could be detected due to the group sequence ($p = 0.9$); we assumed no carryover effect and used the treatment as the sole fixed predictor.

Both medications lowered the IOP significantly compared to baseline (5.4 mmHg for tafluprost and 6.8 mmHg for bimatoprost ($p < 0.0001$)). We also calculated the percent change from baseline in IOP. This was achieved using a generalised linear model with a Gamma error distribution and a logarithmic link function. Compared to baseline, tafluprost reduced the IOP by 27% and bimatoprost by 33% (both $p < 0.0001$).

Since a large proportion of the participants were on bimatoprost before the study, we also explored whether being on bimatoprost could have any additional effect that could bias the results. We used a mixed model with a two-way interaction (between the treatment and the pre-study medication). We could not find any significant effect of being on bimatoprost before the study on the effect of the two drugs used in this study ($p = 0.8757$). We also analyzed the subset of subjects on either latanoprost or bimatoprost, being the two most commonly used medications before enrollment, and found no significant effect ($p = 0.4894$).

We used the same mixed-model analysis to determine if a particular centre had an influence on the medication effect, using the subject as the sole random effect and found the interaction was significant ($p < 0.0001$). Figure 3 shows the IOP values for the different groups at different centres.

Safety results

There were no statistically significant changes in visual field tests, BCVA measurements, or cup-to-disc ratio. One subject in Group 1 showed an increase in the cup-to-disc ratio (from 0.75 to 0.80) at the last visit, but the visual field mean deviation was not decreased compared to baseline (see Table 3). No formal analysis was conducted for the slit lamp assessment as there were too few changes. There was no significant change in hyperemia score between the two treatments in either group (Wilcoxon paired test, $p = 0.78$). The mean hyperemia score was 0.38 (0.05, 0.73) for taflupost and 0.41 (0.07, 0.74) for bimatoprost.

		Score Increase				
		Lid	**Cornea**	**Conjunctiva**	**Iris**	**Lens**
n subjects	Group 1	0	3	2	0	0
	Group 2	2	3	2	0	2
max score		1	2	2	0	1
mode		1	1	1	0	1

Table 3. Score increase from baseline from slit lamp assessment
Lid: periocular hyperpigmentation, hypertrichosis; Cornea: punctate epitheliopathy, keratitis; Conjunctiva: conjunctival hyperemia; Iris: iris hyperpigmentation; Lens: lens opacities

4. DISCUSSION

In this study, patients receiving bimatoprost first then tafluprost did not have a significantly lower IOP at month 3, but did show a significantly higher IOP at month 6. Overall, bimatoprost produced greater IOP reduction compared to tafluprost at 6 months with minimal to no difference in side effects, including hyperemia. At 6 months, bimatoprost lowered IOP by 1.4 mmHg more than tafluprost did from baseline. To the authors' knowledge, SPORT II is the first head-to-head comparison of preservative-free tafluprost and BAK-preserved bimatoprost in glaucoma. However, this is not the first study to show bimatoprost lowered IOP more than a different PGA. Lin et al. conducted a meta-analysis on the efficacy and tolerability of four PGA as first-line therapy.[27] They found 32 randomised, controlled clinical studies; when compared to timolol as the reference drug, bimatoprost achieved the highest treatment success, defined as the proportion of patients who achieved ≥30% reduction in IOP from baseline. In that meta-analysis, the overall IOP reduction for bimatoprost was 1.98 mmHg at 1 month and the results were sustained for 3 months. Our study chose a 6-month primary end point, and our results were similar, with a 1.4 mmHg reduction at 6 months from baseline. Others have also chosen a 6- or 12-month end point, and have also found bimatoprost to lower IOP from baseline of anywhere from 1.6 mmHg to about 10 mmHg.[18,30,31]

El Hajj Moussa et al.[30] concluded there was no significant difference in conjunctival hyperemia when comparing bimatoprost 0.01% (with BAK 0.02%) to latanoprost 0.005% (with BAK 0.02%) and tafluprost 0.0015% (preservative-free) (and travoprost 0.004% (with 0.001% polyquad)). The current study does confirm these findings, while using the same active ingredients, concentrations and preservatives.

The SPORT (I) trial[13] reported significantly more conjunctival hyperemia with preservative-free bimatoprost 0.3 mg/ml (0.03%) compared to preservative-free latanoprost. This difference with the current study might be attributed to the higher concentration of the active ingredient in preservative-free bimatoprost (used in the former trial) compared to BAK-preserved bimatoprost (used in the current trial). Katz et al.[32] showed that bimatoprost 0.01% demonstrated improved tolerability, including less frequent and severe conjunctival hyperemia compared to bimatoprost 0.03%.

The very low hyperemia scores in the current study imply that the subjects enrolled showed an acceptable tolerability profile, in contrast to the subjects enrolled in another trial comparing BAK-preserved and preservative-free bimatoprost-timolol to preservative-free tafluprost-timolol eyedrops,[33] where inclusion criteria included having conjunctival hyperemia and at least one other ocular symptom with preservative-free or BAK-preserved bimatoprost–timolol. In these patients, switching from bimatoprost-timolol to preservative-free tafluprost-timolol significantly reduced conjunctival hyperemia. However, there is a clear selection bias in this trial, as hyperemia with bimatoprost-timolol was an inclusion criterion. The inclusion of subjects already on PGA therapy with good tolerability prior to study participation, may have led to a selection bias in the current study, and can thus possibly explain these low hyperemia scores.

Glaucoma medications preserved with BAK are associated with ocular surface disease, making the use of preservative-free medication an important option for the glaucoma specialist. Several studies have compared preservative-free monotherapy to preserved counterparts and have found that both formulations reduce IOP and have a similar safety profile.[34-36]
However, multiple studies have indicated that preservative-free agents are better tolerated.[21-24,35-39] Uusitalo et al. switched 1,500 patients from a preserved glaucoma medication to preservative-free latanoprost and found that 74% of patients rated preservative-free latanoprost as better (49%) or much better (25%) tolerated than their previous preserved medication.[24] Other studies, however, have found no difference in tolerance between formulations with the same active ingredient.[34,36-39] The latter suggests that, besides the preservatives, also the other constituents as well as the physical-chemical characteristics of the formulation contribute to the tolerability profile of these drops.[5,37,38]
In our study, we compared two different medications (albeit from the same drug class) and two different formulations. Both medications showed statistically and clinically significant IOP lowering. SPORT II found bimatoprost had better reductions in IOP than tafluprost, but there was no difference in reported

tolerability despite the absence of preservatives in tafluprost. Our results differ from other published studies that found preservative-free medications are better tolerated.[21-24,33,37-40] Our results do support the above mentioned previous reports suggesting that the active ingredient may also be implicated in tolerability, along with excipients and pH.[27,29,41] However, it should be noted that the current sample size, based on a clinically relevant difference in mean IOP, should be enlarged to detect significant differences in safety outcomes. Of note, as preservative toxicity is known to be cumulative and dose-dependent,[42-44] a longer treatment period would be needed to consider long-term efficacy and tolerability of the different treatment regimens.

As with any crossover-designed study, there are inherent potential weaknesses, including that these types of studies are of longer duration than parallel-study groups, there may be an increase in patient drop out because of the longer duration and patients who drop out during the crossover (having only completed the first part) offer little to the overall analysis. Carryover effects from previous treatment arm(s) may be difficult to control. Further, data from all time periods in crossover studies are often unavailable for multiple reasons.

However, we adjusted for the centre effect in this study and did not find a carryover effect. As each arm of the study was for a period of 3 months, these effects are probably minimised. Further, we believe the strengths of a crossover study outweigh the weaknesses. Crossover studies are suitable for stable conditions and when interventions are short-lived and not expected to "cure" the condition. Each subject acts as his or her own control in crossover studies, and a smaller number of patients are required in comparison to parallel-group studies. Because these are designed to compare treatments within patients, variation between patients is eliminated.

There were differences in the centre variations at baseline in our study. These could be explained by the differences in distribution of types of glaucoma and in treatment choices. Patients from Centre 1 had lower baseline pressures, which could be due to the high percentage of low-tension glaucoma in this part of Europe. It could also be due to differences in pre-study prostaglandin use, as tafluprost is more readily available in certain countries than others. For example, tafluprost is regularly used and available in Austria, where Centre 5 is located. These baseline differences did not have an effect on outcomes, however, and are only discussed as an interesting side note.

The fact that patients receiving bimatoprost first then tafluprost did not have a significantly lower IOP at month 3 may implicate a limitation on the robustness of the data. However, as the 6-month end point does show a significantly greater IOP reduction by bimatoprost compared to tafluprost, this might suggest better efficacy of bimatoprost.

These potential weaknesses are more than offset by the strengths of the study. First, as mentioned above, the crossover design enables intra-subject differences in treatment arms to be compared in a more precise fashion. The multicentre nature of this study increases the validity of the data by reducing centre-specific effects, without eliminating them entirely. We took several measures to eliminate any potential biases. First, the investigator was masked. Next, the data analysis occurred before unmasking the treatment arms and conducted by an independent statistician who was not involved in patient management.

Further longitudinal study is recommended to assess long-term safety outcomes of preserved/preservative-free PGA formulations and whether additional IOP reduction indeed results in a better control of disease progression.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends:

Figure 1. Cross-over design. The study consisted of four visits: screening (prior to washout), baseline (after 4 weeks washout), after treatment period I (3 months of the first study drug) and after treatment period II (3 months of the second study drug).
V=visit; w=weeks; TUDPF=Tafluprost Unit Dose Preservative Free; BIMMD=Bimatoprost Preserved

Figure 2. Mean IOP at study timepoints.

Figure 3. Box plot representation of IOP values for the different groups at months 3 and 6 at different centers.