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Research Article

Efficacy and safety of travoprost 0.004% compared with tafluprost 0.0015% in patients with primary open-angle glaucoma

Nisha Bachkheti[1]*, Dharamvir Chalia[1], Vijay Kumar Sehgal[2], Sachin Walia[1]

[1]Department of Ophthalmology, Government Medical College, Patiala, Punjab, India, [2]Department of Pharmacology, Government Medical College, Patiala, Punjab, India

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***Correspondence to:**
Nisha Bachkheti,
Email: nisha_bach@yahoo.com

ABSTRACT

Background: This prospective, open, randomized, parallel-group, comparative study is to evaluate the efficacy and side-effect profile of travoprost (TRAV) 0.004% compared with tafluprost (TAF) 0.0015% in patients with primary open-angle glaucoma (POAG) over 12 weeks. A total of 80 patients of POAG selected and were randomized to either TRAV or TAF monotherapy administered once daily in the evening for 12 weeks.
Methods: The study was conducted on 80 cases of POAG, in which patients were randomized to either TRAV or TAF monotherapy administered as 1 drop daily in the evening for 12 weeks. Intraocular pressure (IOP) was measured (8 am, 12 noon and 4 pm) at each visit, slit-lamp bio-microscopy was done and side effects noted.
Results: The mean IOP reduction in TRAV group decreased from 27.58±2.30 to 19.03±2.326 thus resulting in fall of 8.55 (31.0%) and in TAF group it decreased from 27.38±2.676 to 20.58±2.827 resulting in fall of 6.8 mm Hg (24.8%) was significant ($p<0.05$). In both treatment groups, the most frequently reported adverse event at 12 weeks was red eye, noted in, 9 (22.5%) and 7 (17.5%) cases of TRAV and TAF groups respectively, though the difference was not statistically significant.
Conclusion: TRAV 0.004% monotherapy produced lower diurnal IOP than TAF 0.0015% in patients with POAG and exhibited a similar safety profile.

Keywords: Primary open-angle glaucoma, Intraocular pressure, Tafluprost, Travoprost

INTRODUCTION

Elevated intraocular pressure (IOP) is considered a key risk factor for the progression of glaucoma.[1,2] As such, IOP reduction is a primary objective of the pharmacologic treatment of glaucoma.[3] Several studies have demonstrated that IOP reduction does, in fact, slow glaucoma progression.[4-6]

Prostaglandin analogs are among the most potent IOP-lowering therapies currently available.[3] These include the latanoprost, travoprost (TRAV), tafluprost (TAF), and bimatoprost. Prostaglandin analogs have demonstrated greater IOP-lowering efficacy than beta-adrenergic blockers[7] and, for that reason, are commonly used as first-line therapy against glaucoma.[3] In addition, all prostaglandin analogs have convenient once-daily dosing, whereas some other IOP-lowering therapies require dosing 2-3 times daily.

In 1996, latanoprost 0.005% was the first prostaglandin analog to be approved by the US Food and Drug Administration for the treatment of ocular hypertension and open-angle glaucoma. TRAV 0.004% another prostaglandin analog was approved in 2001 for a similar indication.[8] TAF 0.0015% is the most recently released prostaglandin analog, being approved in Europe in 2008.

TAF is a prostaglandin analogue, a selective FP prostanoid receptor agonist. It is believed to reduce IOP by increasing uveoscleral outflow of aqueous humor. TAF was found to be non-inferior to timolol 0.5% and latanoprost.[9,10] The addition of TAF to timolol was superior to timolol alone.[11]

It is well-established that IOP is subject to the circadian variation in both healthy individuals and those with glaucoma, although IOP fluctuation is magnified in glaucomatous eyes.[12] Thus, effective once-daily IOP-lowering medications

must have consistent efficacy throughout the day to reduce the risk of IOP spikes, which have been associated with the progression of glaucoma.[13] TRAV 0.004% has not only demonstrated significant reductions in IOP throughout a 24 hr period, but also it has shown superior late afternoon (4 pm and 6 pm) efficacy compared with that of latanoprost 0.005%.[14,15] Data from a Phase III trial suggest that TAF 0.0015% may have efficacy similar to that of latanoprost.[9]

Thus, due to the apparent superiority of IOP control by TRAV over latanoprost in the late afternoon, it is reasonable to speculate that TRAV and TAF may show a pattern of IOP-lowering efficacy that is similar to that of TRAV and latanoprost. However, due to the recent addition of TAF to the marketplace, limited clinical information currently exists directly comparing TAF with other prostaglandin analogs. The aim of this study was to compare the diurnal IOP-lowering efficacy and safety of TRAV 0.004% and TAF 0.0015% in patients with primary open-angle glaucoma (POAG).

METHODS

The study was conducted on 80 cases of POAG attending Ophthalmology Out Patient Department; Rajindra Hospital, Patiala. One subject will be taken as one case.

An informed consent was taken from the patients included in the study. Detailed ocular and medical history was noted along with the past treatment history and then required ophthalmological examination was done. The patients were randomly assigned to one of the two treatment groups, each having a sample size of 40 patients.

Group 1: TRAV 0.004% with benzalkonium (BAK) chloride as a preservative, one drop administered at 8 pm every night.

Group 2: TAF 0.0015% administered with BAK chloride as preservative, one drop administered at 8 pm every night.

These drugs are freely available in the market.

Inclusion criteria

1. Subjects will include POAG cases either already on treatment or newly diagnosed cases with IOP >21 mm Hg and showing mild functional and structural damage.
2. Cases of established POAG were eligible for the study if there IOP was >21 mm Hg after discontinuation of all ocular hypotensive medication (The washout period will be as follows, i.e., miotics and carbonic anhydrase inhibitors will be discontinued for 5 days, alpha and beta adrenergic agonists for 14 days, and beta blockers, prostaglandin analogues and combination drugs for 28 days).
3. Open angle on gonioscopy.
4. Men and women 18 years and older.
5. Ability to meet the follow-up requirements for a minimum of 12 weeks.
6. Written informed consent for the study.

Exclusion criteria

1. H/O angle closure glaucoma/secondary glaucoma.
2. History of diabetes, hypertension, bronchial asthma or any other chronic systemic illness.
3. Patients having any other ocular disorder.
4. History of ocular trauma or intraocular surgery.
5. Cup disc ratio >0.9 and advanced damage on visual fields.
6. Pregnant and lactating females.
7. Hypersensitivity or contraindications to components of study medication.

Study eye

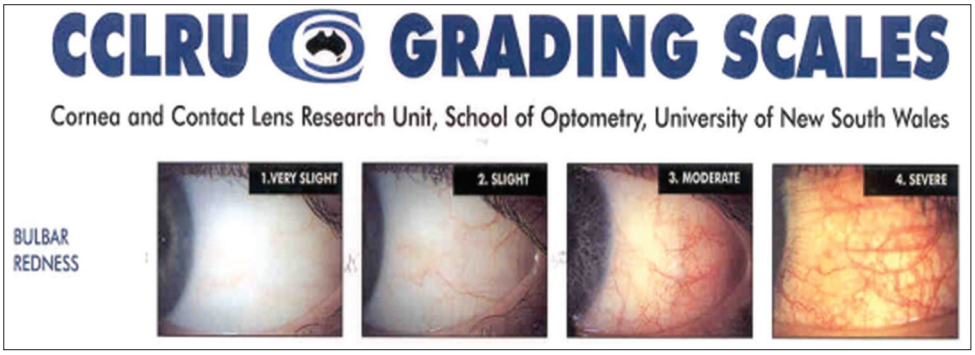
In both the groups, the eye that was affected was considered as the study eye. If both the eyes were involved then the eye with more damage at presentation was treated as study eye or if the eyes had similar damage then by convention right eye will be studied. The other eye will be observed and managed as appropriate but will not figure in any of the published results.

All patients will be subjected to the following examination and tests at baseline and 4 weeks, 8 weeks and 12 weeks after starting the study treatment.

- Visual acuity and refraction.
  Visual acuity will be recorded using Snellens acuity chart.
- Eyelashes, lid and adnexa (digital photography was done).
- Conjunctiva with evaluation of hyperemia using cornea and contact lens research unit (CCLRU) grading scale. This photographic scale was developed by the CCLRU at the University of New South Wales, Australia[16] and comprises four images that increase in severity of the condition, and are labeled as follows: (1) Very slight; (2) slight; (3) moderate; (4) severe. The study eye of each subject will be examined using a slit-lamp bio-microscope (×10 magnification) under diffuse, white illumination. The subject's position of gaze will be directed to allow grading of four quadrants: superior, nasal, inferior, and temporal. The bulbar redness score will be defined as the average of the scores of the four quadrants.
- Cornea, iris, pupil and lens.
- Anterior chamber with cells and flare graded based on standardization of uveitis nomenclature working group.[17]
  Grading scheme for anterior chamber cells:

Grade	Cells in field*
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

(*Field size is a 1 mm×1 mm slit beam)



Grading scheme for anterior chamber flare:

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

- Gonioscopy
  Grading was done using RP centre system:
  Grade 0 - No dipping of beam
  Grade 1 - Dipping of beam
  Grade 2 - Anterior (non-pigmented) trabecular meshwork
  Grade 3 - Posterior pigmented trabecular meshwork
  Grade 4 - Scleral spur
  Grade 5 - Ciliary body band
  Grade 6 - Root of iris.
  Patients having angle of Grade 3 or more were taken in the study.
- IOP measurement at 8 am, 12 noon, 4 pm using Goldman applanation tonometer
- Dilated fundus examination using 90D lens
- Visual field testing was done with Humphrey Field Analyzer. Achromatic Standard 30-2 Swedish Interactive Threshold Algorithm visual fields were obtained with stimulus size III. Only patients with reliable fields (fixation losses <33%, false positive <20% and false negative <20%) were included in the study. A normal visual field is defined as one having glaucoma hemifield test (GHT) within normal limits and a pattern standard deviation (PSD) with p>5% on two consecutive examinations
- Pulse and blood pressure.

Diagnostic criteria for glaucomatous disc damage (structural damage)

1. Neuroretinal rim if it does not follow ISNT rule
2. Vertical C:D ratio ≥0.6 in normal size and normal shape disc. Clinically disc size was judged by the 5° aperture of Welch Allyn direct ophthalmoscope, which has a diameter of 1.7 mm. It was used to get a rough idea whether the disc was larger or smaller than that
3. Asymmetrical C: D ratio more ≥0.2
4. Acquired optic nerve pit or notch, splinter haemorrhage and peripapillary atrophy
5. Retinal nerve fibre layer damage.

The criteria of ISNT rule was necessary in every case along with two more criteria out of the 4 for the diagnosis of glaucomatous optic neuropathy.

If the disc showed a notch in the superotemporal or inferotemporal area no other criteria was required. The co-relationship between the optic nerve head damage and the visual field damage was utmost important, if the visual field defects were present.

Diagnostic criteria for glaucomatous disc damage (functional damage)

Minimum criteria for diagnosing acquired glaucomatous damage were labelled using Hodapp-Parrish-Anderson[18] criteria for glaucomatous damage:

- A GHT outside normal limit
  Or
- A cluster of three or more nonedge points in a location typical for glaucoma, all of which are depressed on the pattern deviation plot at a p<5% level and one of which is depressed at a p<1% level on two consecutive fields
  Or
- A corrected PSD that occurs in less than 5% of normal fields on two consecutive fields
  Reliable fields will be those with a fixation loss rate <33% and false positive and false negative rate ≤20%.
  Severity of damage was classified as early, moderate and severe defect on the basis of following points
- Early defect: Damage should be neither extensive nor near fixation. The following three conditions should be met:
  1. The mean deviation index (MD) is <6 dB
  2. On the pattern deviation plot, fewer than 25% (18) of the points are depressed below the 5% level and fewer than 10 points are depressed below the 1% level.
  3. No point in the central 5° has a sensitivity of <15 dB.
- Moderate defect: Damage may be significant, but there

should not be profound central field damage, and there should not be significant central field damage in both hemifields. The following four conditions should be met:

1. The mean defect is <−12 dB.
2. On the pattern deviation plot, fewer than 50% (37) of the points are depressed below the 5% level and fewer than 20 points are depressed below the 1 % level.
3. No point in the central 5° has a sensitivity of 0 dB.
4. Only one hemifield may have a point with sensitivity of <15 dB within 5° of fixation.

- Severe defect: Any of the following findings indicates severe field loss:
  1. The mean defect is >12 dB.
  2. On the pattern deviation plot, more than 50% (37) of the points are depressed below the 5% level or more than 20 points are depressed below the 1% level.
  3. There are points within the central 5° with sensitivity <15 dB in both hemifields.

All data will be recorded and analyzed using appropriate statistical tests.

RESULTS

The mean age of the patients in the groups TRAV and TAF were 68.18±8.4 years and 66.43±8.5 years, respectively. The groups were statistically similar at baseline with regards to age as p value b/w groups by is 0.357 (p>0.05) (Table 1).

There were total 39 male and 41 female patients. The distribution of male and female patients was similar in the three groups with the difference being statistically insignificant (p>0.05, Fisher's exact test) (Table 2).

Table 1: Age distribution in groups.

Group	Mean age (years)	SD (years)
TRAV	68.18	8.4
TAF	66.43	8.5
p value	0.357	

TRAV: Travoprost, TAF: Tafluprost, SD: Standard deviation

Table 2: Gender distribution in groups.

Sex	N (%)	
	Group TRAV	Group TAF
Male	18 (45)	21 (52.5)
Female	22 (55)	19 (47.5)
p value	0.65	

TRAV: Travoprost, TAF: Tafluprost

Table 3: Distribution of MD on Humphery visual field in both groups at baseline.

VF-Baseline	MD baseline	SD
Group TT	−5.31	2.04
Group LT	−5.13	1.73
p value	0.67	

SD: Standard deviation, MD: Mean deviation

The mean defect noted in the visual fields was mild defect in the two groups with MD being −5.31 and −5.13 in TRAV and TAF groups. The difference was statistically not significant with p>0.05 (Table 3).

The baseline mean IOP between the three groups was comparable with p>0.05 at 8 am, 12 noon and 4 pm (Table 4).

There was significant difference in the mean IOPs' between the two groups measured at 8 am at 4 weeks, 8 weeks and 12 weeks follow-up visits (p<0.05) with lower mean IOP in TRAV group (Table 5).

There was significant difference in the mean IOPs' between the two groups measured at 12 noon at 4 weeks, 8 weeks and 12 weeks follow-up visits (p<0.05) with lower mean IOP in TRAV group (Table 6).

There was significant difference in the mean IOPs' between two groups measured at 4 pm at 4 weeks, 8 weeks and 12 weeks follow-up visits (p<0.05) with lower mean IOP in TRAV group (Table 7).

The most frequently reported adverse event at 12 weeks was red eye. Grade 1 (20%) and Grade 2 (2.5%) in the TRAV group, and Grade 1 (17.5%) in the TAF group and the difference is statistically insignificant (p>0.05) (Table 8).

Some other side-effects such as dry eyes, watering, itching were seen, but the difference in these side-effects was not clinically significant between the two treatment groups (Table 9).

DISCUSSION

Although there are various risk factors associated with development and progression of glaucoma, but IOP is the most important and easily modifiable risk factor. IOP can be managed both medically and surgically. Medical management is usually preferred as the initial treatment as it avoids surgical risks.

This clinical trial has compared the treatment with TRAV 0.004% with that of TAF 0.0015% in patients with POAG, both TRAV and TAF demonstrated good IOP control. The mean decrease in IOP at 12 weeks by the TRAV and TAF was 8.55±2.012 mm Hg (31%) and 6.80±1.910 mm Hg (24.8%) respectively at 8 am. Similar results were obtained at 12 noon and 4 pm. These data suggest that TRAV provides a modest, but significant advantage in IOP control over TAF. Of note is the fact that, similar to previous studies comparing TRAV and latanoprost,[14,15] TRAV in this study produced superior IOP control in the late afternoon (i.e., at 4 pm).

Table 4: Comparison of mean IOP of both groups at baseline.

Time	Mean±SD		p value	Significance
	TRAV	TAF		
8 am	27.58±2.308	27.38±2.676	>0.05	NS
12 noon	27.35±2.32	27.38±2.67	>0.05	NS
4 pm	27.45±2.30	27.25±2.93	>0.05	NS

IOP: Intraocular pressure, SD: Standard deviation, NS: Not significant, TRAV: Travoprost, TAF: Tafluprost

Table 5: Comparison of mean IOP of both groups at 8 am.

Interval	Mean±SD		p value	Significance
	TRAV	TAF		
Baseline	27.58±2.308	27.38±2.676	>0.05	NS
4 weeks	19.43±2.037	20.95±2.708	<0.05	S
8 weeks	19.23±2.178	20.68±2.454	<0.05	S
12 weeks	19.03±2.326	20.58±2.827	<0.05	S

IOP: Intraocular pressure, SD: Standard deviation, TRAV: Travoprost, TAF: Tafluprost, NS: Not significant, S: Significant

Table 6: Comparison of mean IOP of both groups at 12 noon.

Interval	Mean±SD		p value	Significance
	TRAV	TAF		
Baseline	27.35±2.32	27.38±2.67	>0.05	NS
4 weeks	19.30±2.20	20.83±2.59	<0.05	S
8 weeks	19.00±2.20	20.45±2.21	<0.05	S
12 weeks	18.90±2.16	20.45±2.73	<0.05	S

IOP: Intraocular pressure, SD: Standard deviation, TRAV: Travoprost, TAF: Tafluprost, NS: Not significant, S: Significant

Table 7: Comparison of mean IOP of both groups at 4 pm.

Interval	Mean±SD		p value	Significance
	TT	LT		
Baseline	27.45±2.30	27.25±2.93	>0.05	NS
4 weeks	19.23±1.88	20.75±2.67	<0.05	S
8 weeks	19.10±2.09	20.55±2.57	<0.05	S
12 weeks	18.80±2.37	20.33±2.82	<0.05	S

IOP: Intraocular pressure, SD: Standard deviation, NS: Not significant, S: Significant

Table 8: Incidence of red eye among patients in the two treatment groups.

Red eye	TAF	TRAV (%)	p value (Fisher exact test)
None	33 (82.5)	31 (77.5)	0.78
Very slight Grade 1	7 (17.5)	8 (20.0)	
Slight Grade 2	0 (0)	1 (2.5)	
Moderate Grade 3	0	0	Not applicable
Severe Grade 4	0	0	

TRAV: Travoprost, TAF: Tafluprost

No unexpected safety concerns with either TRAV or TAF monotherapy were observed during the course of this clinical trial. Hyperemia is a class effect of prostaglandin analogs,[19] and both TRAV and TAF induced similarly modest levels of hyperemia. The most common side-effect noted was red eyes with 22.5% and 17.5% patients having either Grade 1 or Grade 2 red eye in TRAV and TAF group, respectively.

The differences in mean IOP between TRAV and TAF were statistically significant, although they were small (1.5 mm Hg). The clinical significance of the superior IOP control by TRAV is unclear, Konstas et al. have demonstrated that small differences in IOP (in 1 mm Hg increments) can have a substantial impact on the likelihood of glaucoma progression within certain IOP ranges.[20]

We recognize the limitations of this study. First, this is a single-centre study with a limited number of patients.

Table 9: Incidence of other side effects among patients in the two treatment groups.

Side effect	TRAV (%)	TAF (%)	p value (Fisher's exact test)
Dry eyes	9 (22.5)	5 (12.5)	0.37
Itching	5 (12.5)	6 (15.0)	1.00
Ocular discomfort	3 (7.1)	4 (9.3)	1.00
Watering	0	0	Not applicable
SPKs	0	0	
Dark eye circles	0	0	
Eyelash lengthening	0	0	
CME	0	0	

TRAV: Travoprost, TAF: Tafluprost, CME: Cystoid macular edema, SPK: Superficial punctate keratitis

Second, our study was limited by its short time frame. 12 weeks could be sufficient to evaluate changes in IOP levels and to assess the presence or absence of many potentially adverse events. However, longer follow-up periods are required to assess certain side-effects like eyelash lengthening, iris pigmentation and cystoid macular edema. Third, our study did not provide information about IOP during the night, and it is well known that the risk of glaucoma progression is increased, at least in some cases, by the fact that IOP may be higher during the night.

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