ORIGINAL RESEARCH

Use of Latanoprostene Bunod as Adjunctive Glaucoma Therapy in Refractory Glaucoma

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Abstract

Aim: To investigate the long-term efficacy of adjunctive use of latanoprostene bunod (LBN), a new nitric oxide donating prostaglandin medication, in refractory cases of glaucoma at a tertiary care center.

Materials and methods: A review for patients who received add-on LBN was conducted from 1st January 2018 to 31st August 2020. A total of 33 patients (53 eyes) met the inclusion criteria of being on ≥3 topical medications, having an intraocular pressure measurement prior to starting LBN, and having adequate follow-up. Baseline demographics, prior treatments, adverse effects, and intraocular pressures measured at baseline, 3, 6, and 12 months were recorded.

Results: Mean baseline intraocular pressure (IOP) [mm Hg ± standard deviation (SD)] was 19.9 ± 6.0. At 3 months, 49 eyes had a mean IOP of 17.3 ± 5.5 ($p < 0.01$) with an absolute reduction of 2.6 ± 6.6 and a percent reduction of 9 ± 28%. At 6 months, 35 eyes had a mean IOP of 17.2 ± 4.7 ($p < 0.01$) with an absolute reduction of 3.6 ± 7.4 and a percent reduction of 11 ± 30%. At 12 months, 28 eyes had a mean IOP of 16 ± 4.5 ($p < 0.01$) with an absolute reduction of 5.8 ± 7.4 and a percent reduction of 19 ± 38%. Over the course of the study, 18 eyes were lost to follow-up. Three eyes had a laser trabeculoplasty, and four eyes required incisional surgery. No eyes discontinued the medication due to adverse effects.

Conclusion: Adjunctive use of LBN in refractory glaucoma showed clinically and statistically significant IOP reductions at 3, 6, and 12-month time points. IOP reduction in patients was stable throughout the course of the study, with the largest decreases seen at the 12-month interval.

Clinical significance: LBN was well tolerated by patients and may be useful as an additive agent in providing long-term intraocular pressure reduction for patients with severe glaucoma on maximal therapy.

Keywords: Glaucoma, Intraocular pressure, Latanoprostene bunod, Prostaglandin analog.

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Introduction

Glaucoma is a progressive, multifactorial eye disease that causes irreversible damage to the optic nerve and is one of the leading causes of visual impairment worldwide. Its insidious course makes disease detection and treatment difficult, requiring lifelong adherence to treatment to prevent progression.[1,2] Currently, the only treatment proven to slow the rate of glaucomatous progression is lowering IOP.[3–6] While there are several effective ways to reduce intraocular pressure, including medications, laser treatment, and surgical management, pressure-lowering eye drops are often the first line and mainstay treatment for adequate intraocular pressure control.[7] Clinical trial data often reflect a direct comparison of a study drug to a control. Upon approval, many novel medications are utilized as adjunctive agents, often with more complex medication regimens. Our study aims to investigate the use of LBN in patients with refractory glaucoma who are on multiple medications.

Due to the complexity of glaucoma management, patients often require combination therapy of more than one class of medication to adequately control IOP.[8] The new Food and Drug Administration-approved topical agents have sought to address some of the limitations of older medications, such as side effects, lower efficacy, and increased dosing frequency. One of these agents, LBN was approved in 2017 for the treatment of open-angle glaucoma and ocular hypertension.

Latanoprostene bunod (LBN) is a modified prostaglandin with a nitric oxide donating moiety. LBN lowers IOP *via* two different pathways: the prostaglandin analog, latanoprost acid, increases uveoscleral outflow while nitric oxide causes relaxation of smooth muscles and vasodilation in various tissues of the eye, including the trabecular meshwork, Schlemm's canal, and the ciliary body.[9–12] Clinical trials have only compared LBN as monotherapy to one other agent. The VOYAGER study compared LBN to once-daily dosing of latanoprost 0.005% while the APOLLO, LUNAR, and JUPITER studies compared LBN to twice daily dosing of timolol 0.5%. Used as a monotherapy, LBN was found to reduce IOP significantly more than latanoprost 0.005% or timolol 0.5%. The safety profile and long-term efficacy of LBN were established in the phase three APOLLO, LUNAR, and JUPITER studies, confirming its use as an IOP-lowering agent that is well-tolerated and clinically safe for patients with open-angle glaucoma and ocular hypertension.[13–16]

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While clinical trial information is vital, it does not translate directly to clinical use. There are still substantial hurdles to using LBN; many times, it is used adjunctively or in place of other agents for patients who have failed multiple modalities of therapy. Currently, real-world application data of LBN as adjunctive therapy is limited. To date, only two publications have evaluated the application of LBN in a real-world setting; both studies had high variability in the frequency of follow-ups and overall duration of follow-ups.[17,18] The purpose of this study is to further build on the scarcity of literature on the use and long-term efficacy of LBN as adjunctive therapy in patients with refractory cases of glaucoma at a tertiary care glaucoma clinic.

Materials and Methods

A retrospective review of records identified patients who were prescribed LBN 0.024% at Rutgers New Jersey Medical School, Institute of Ophthalmology and Visual Science, Newark, New Jersey, United States of America, a tertiary care center, from 1st January 2018 to 31st August 2020. Patient electronic records were reviewed to determine whether they met the inclusion criteria. For inclusion, patients had to have a confirmed clinical diagnosis of glaucoma (primary or secondary based on clinical exam, structure, and function testing), utilize three or more topical agents, and have two documented IOP measurements prior to starting LBN as adjunctive therapy. Patients were excluded if there was an inadequate follow-up after starting LBN (zero visits after starting), if they had any type of surgery after starting LBN, or if they were unable to take LBN for any reason. Baseline characteristics that were recorded included age, gender, ethnicity, mechanism of glaucoma and prior topical, laser, and surgical treatments.

After initiating LBN treatment, follow-up data were recorded at 3, 6, and 12-month intervals with ±4-week windows. IOP was measured with Goldmann applanation tonometry. In addition to measuring IOP, at each follow-up visit, ocular medications, adverse events, and reasons for discontinuation were recorded. Primary outcomes included absolute and relative IOP reduction from baseline as well as percent IOP reductions. Paired student's *t*-tests were used for statistical analysis, and statistical significance was set at $p = 0.01$ using Bonferroni correction.

Approval for this study was received from the Institutional Review Board at Rutgers New Jersey Medical School, Institute of Ophthalmology & Visual Science, Newark, New Jersey, United States of America. The study followed the tenets of the Declaration of Helsinki and was conducted in accordance with the Health Insurance Portability and Accountability Act.

Results

A total of 45 patients were prescribed LBN during the study period, of which 33 patients (53 eyes) met the inclusion criteria. Thirty-seven eyes had LBN started as adjuvant therapy, and 16 eyes had LBN substituted for a prostaglandin analog. In total, 33 eyes did not meet the inclusion criteria of utilizing three or more topical agents, and another four eyes were excluded due to inadequate follow-up after LBN prescription (zero visits after starting LBN). In total, 20 had both eyes enrolled in the study, while 13 patients had only one eye enrolled in the study.

The study population included 15 (42%) male and 21 (58%) female patients with a mean age of (±SD) 72.1 ± 11.0. A total of 18 (50%) patients were Caucasian, 15 (42%) patients were African American, two (6%) were Indian American, and one (3%) was Asian (Table 1). A total of 45 (85%) eyes had primary open-angle glaucoma, six (11%) eyes had neovascular glaucoma, and two (4%) eyes had uveitic glaucoma. Most patients had late-stage glaucoma, with 40 (73%) eyes diagnosed as severe. Around 14 (25%) eyes were diagnosed with moderate glaucoma, and one (2%) eye was diagnosed with mild glaucoma. A total of 31 (55%) eyes had no prior glaucoma laser or surgical treatment, 11 (21%) eyes had selective laser trabeculoplasty, nine (17%) eyes had seton implantation, two (4%) eyes had a trabeculectomy, and one (4%) eye had trabecular bypass implants (iStent, Glaukos, CA) (Table 2).

The mean baseline IOP (mm Hg ± SD) was 19.9 ± 6.0 (53 eyes). At 3 months, 49 eyes had a mean IOP of 17.3 ± 5.5 ($p < 0.01$) with an absolute reduction of 2.6 ± 6.6 and a percent reduction of 9 ± 28%. About 35% of eyes achieved a 20% reduction from baseline, 22% of eyes achieved a 30% reduction from baseline, and 10% of eyes achieved a 40% reduction from baseline. At 6 months, 35 eyes had a mean IOP of 17.2 ± 4.7 ($p < 0.01$) with an absolute reduction of 3.6 ± 7.4 and a percent reduction of 11 ± 30%. Around 40% of eyes achieved a 20% reduction from baseline, 29% of eyes achieved a 30% reduction from baseline, and 17% of eyes achieved a 40% reduction from baseline. At 12 months, 28 eyes had a mean IOP of 16 ± 4.5 ($p < 0.01$) with an absolute reduction of 5.8 ± 7.4 and a percent

Table 1: Patient demographics

	Mean	*SD*
Age	72.1	11
	n	%
Gender		
Male	15	41.7%
Female	21	58.3%
Race		
Caucasian	18	50.0%
Black	15	41.7%
South Asian	2	5.6%
East Asian	1	2.8%

Table 2: Patient characteristics

	n	**%**
Eyes	53	100%
Glaucoma		
Primary open angle	45	84.9%
Neovascular	6	11.3%
Uveitic	2	3.8%
Severity		
Mild	1	1.9%
Moderate	14	26.4%
Severe	40	75.5%
Surgical or laser treatment		
Selective laser trabeculoplasty	11	20.8%
Seton implantation	9	17.0%
Trabeculectomy	2	3.8%
iStent	1	1.9%
None	31	58.5%

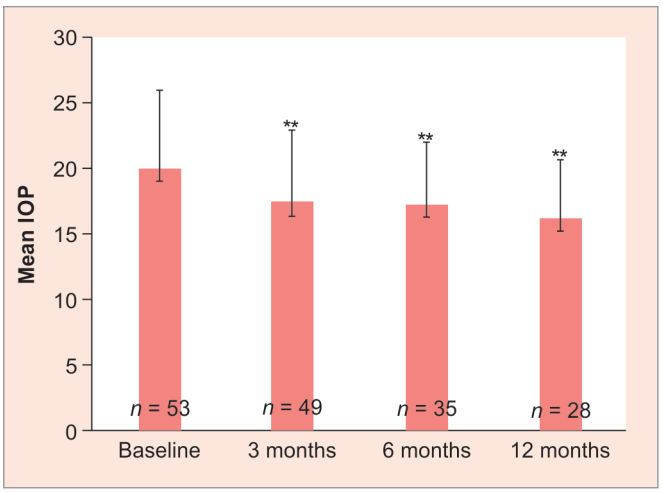

Fig. 1: Mean IOP of all patients. **Indicates $p < 0.01$ compared to baseline IOP; IOP, intraocular pressure

reduction of 19 ± 38%. 57% of eyes achieved a 20% reduction from baseline, 39% of eyes achieved a 30% reduction from baseline, and 25% of eyes achieved a 40% reduction from baseline (Fig. 1).

Throughout the course of the study, seven (13%) eyes were removed due to surgical intervention. Three (5.7%) eyes had a laser trabeculoplasty, and four (7.5%) eyes required incisional surgery. We did not observe any medication discontinuation due to adverse events. Over the course of observation, 18 (34%) eyes were either lost to follow-up or excluded due to further laser or incisional surgery.

Discussion

The use of LBN as adjunctive therapy in a clinical setting resulted in statistically significant IOP reductions at all follow-up time points for patients who have been prescribed this new medication. As with many novel medications, formulary restrictions may prevent prescribing them as first-line therapy. Clinicians often use new medications, like LBN, as a substitute or adjunctive therapy in various more advanced clinical settings. Registration trials provide no data in that context. In our study, at the 3, 6, and 12-month follow-up visits, IOPs were reduced by 2.76, 2.92, and 4.63 mm Hg compared to baseline, respectively ($p < 0.0001$). Previous clinical trials evaluated LBN as monotherapy and found LBN to be superior to timolol or latanoprost alone in reducing IOP.[19] However, as mentioned above, LBN monotherapy is often less feasible or used in clinical practice at this time, and achieving similar results while being used as an adjunctive agent is not well studied. A prior study suggested adding a third or fourth topical agent diminished its effect in reducing IOP.[20] In this present study, all patients were on three or more existing glaucoma medications before LBN was added on, suggesting LBN may still provide clinically significant IOP reduction when used in combination with other medications and with maximal therapy.

Intraocular pressure (IOP) reduction in patients was stable throughout the course of observation. Although patients achieved the greatest IOP reduction at the 12-month follow-up time, we suspect selection bias played a role, and this was likely due to the elimination of eyes, which required further surgical intervention. These eyes were removed because they did not receive clinically meaningful IOP reductions for their respective stage of disease and required further intervention beyond add-on topical LBN. At 3 months, 92.4% of eyes were still included in the analysis, while at 6 months, 66% of eyes were still included, and at 12 months, 53% of eyes were. Nevertheless, IOP was still significantly reduced at the 3, 6, and 12-month follow-up times ($p < 0.01$).

This finding is supported by a recent study that evaluated LBN's use as an adjunctive agent. In that study, baseline IOP prior to starting LBN was 19.4 mm Hg, and at the single follow-up (mean 79.4 days), there was an absolute reduction of 2.9 mm Hg.[17] Our study had a similar starting baseline IOP with similar absolute and percent reductions in IOP. However, our study provides additional value in examining IOP reduction over a longer period (365 days) and over multiple visits, allowing us to more effectively capture IOP reduction trends and map LBN's efficacy. In addition, that study primarily evaluated LBN's use as monotherapy or dual therapy, with 71% of patients on either one or two drops. In the real world, LBN is likely to be used as adjunctive therapy in patients who are already on a fixed combination or multiple drops for glaucoma.

In a separate study, LBN was found to significantly lower IOP in patients prescribed multiple medical therapies (3.2 medications).[18] Baseline IOP prior to starting LBN was 14.9 mm Hg; at the 1-month follow-up (mean 38.7 days), there was an absolute reduction of 2.1 mm Hg (14% reduction), while at the end of the study (mean 235.9 days), there was an absolute reduction of 2.5 mm Hg (16% reduction). While our study started initially with a higher baseline IOP and saw slightly higher absolute reductions of IOP, by the end of the follow-up period, both studies achieved a similar percent reduction in IOP. However, our study provides additional consistency of follow-up at three different time points, allowing us to capture the long-term effects of IOP reduction more accurately. In their study, the first follow-up after LBN was prescribed was within 7 days of starting, and the second follow-up lumped together all patients at the latest time point where they were still on LBN, which was anywhere from 39 to 624 days. Furthermore, our study population had a larger proportion of Caucasians and African Americans, two races with the highest prevalence of glaucoma. Finally, our study population had a higher proportion of people with severe glaucoma, which is particularly important because LBN is often used in patients who have failed multiple medical modalities of treatment.

In addition, results suggest that LBN can be useful in treating late-stage glaucoma. In our study population, 73% of eyes were classified as having clinically determined severe glaucoma. LBN is useful in treating earlier stages of glaucoma, as 25% of eyes were classified as having moderate glaucoma, and 2% of eyes were classified as having mild glaucoma. This is supported by studies that found LBN to have IOP-lowering effects on both naive eyes and eyes on multiple glaucoma medications.[18,21]

Like in the registration trials and other studies looking at LBN, we found that LBN was safe to use and was well-tolerated by patients. In our study, there were no patients that discontinued the medication due to adverse effects. However, LBN was discontinued in several patients because the IOP response to treatment was not sufficient to achieve IOP goals. In these seven refractory eyes (13%), surgical management was indicated to control IOP, with three eyes undergoing laser trabeculoplasty and four eyes requiring incisional surgery. This indicates that in refractory cases, there will still be a subset of patients who do not achieve clinically determining treatment success with LBN add-on therapy and will go on to require further surgical interventions.

While this study helps provide additional data on the use, efficacy, and overall safety of LBN as an adjunctive agent in a clinical

setting, it is still limited in several ways. Due to the retrospective nature of data collection, there was no control group to compare to the patients taking LBN. In addition, many of the patients had both eyes enrolled in this study, so some of the IOP reduction may be due to a concordant response. Similarly, the use of antihypertensives or vasodilators along with LBN may have affected overall IOP. Data on existing patient diseases or systemic medications were not recorded or analyzed. In clinical care, medication adherence is often assessed *via* self-reporting, which tends to overestimate adherence behavior. In addition, many factors influence medication adherence, including the complexity of regimens which may have influenced our results.

Finally, we decided to exclude patients who had under three glaucoma medications because we wanted to assess the efficacy of LBN, as it is often used clinically in the real world as an adjunctive medication in more severe glaucoma. Clinical trials have already proven its efficacy as monotherapy, but there have been few studies assessing its use as an adjunctive agent for patients already on maximum therapy. In clinical practice, it is less likely at present that LBN would be prescribed first or as a monotherapy to treat glaucoma due to the cost and current formulary restrictions. As formulary coverage expands for LBN, it becomes more likely to be prescribed as first-line or for patients on fewer medications. Thus, we felt that including patients using LBN who had under three glaucoma medications would not accurately capture its potential to be used when traditional glaucoma medications fail. Overall, while this study sheds light on LBN's efficacy and safety in a real-world clinical setting, this study has its own inherent limitations and should be interpreted within its context.

Conclusion

The data suggest that LBN can be useful as an additive agent to lower IOP for patients with severe glaucoma on maximal therapy. The safety profile of LBN is excellent and has been well-tolerated by patients. Notably, IOP lowering persisted through the 12-month follow-up period. Further research on the use of LBN as an adjunctive agent is necessary to fully assess its efficacy.

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