Adjunctive glaucoma therapy use associated with travoprost, bimatoprost, and latanoprost

David Covert and Alan L. Robin

Alcon Research Ltd., Fort Worth, TX, USA
Johns Hopkins University, Baltimore, MD, USA

Purpose: This study contrasts the utilization of adjunctive medication associated with travoprost, bimatoprost, or latanoprost, as primary glaucoma therapies.

Methods: Patients in the Medco Health database who initiated prostaglandin analog therapy on travoprost, bimatoprost or latanoprost between January 1, 2002 and July 31, 2002 were selected if they had no prostaglandin analog use in the prior 6 months. Patients were also required to have 12 months of prostaglandin therapy subsequent to the initial prescription. Data were available through July 31, 2003. The t-test and chi-square were used where appropriate to calculate p-values and assess significant differences.

Results: A total of 13171 benefit-eligible subjects were identified of which 8381 (64%), 2637 (20%), and 2153 (16%) patients were treated with latanoprost, bimatoprost, and travoprost, respectively. There were no significant differences in mean age or gender between the three study groups with the exception that latanoprost patients were statistically older than travoprost patients (69.0 vs. 68.0). This was not considered a clinically meaningful difference. Overall, patients using travoprost or bimatoprost had a significantly lower rate of adjunctive medication use compared to patients starting on latanoprost monotherapy (22.5%, 23.2%, and 30.2 %, respectively). Therefore, for every 14 patients treated with latanoprost instead of travoprost or bimatoprost, one additional patient would be expected to need adjunctive therapy with another agent. The difference between travoprost and bimatoprost patients was not significant.

Conclusions: The use of adjunctive medications to control intraocular pressure was significantly higher for latanoprost patients compared to travoprost and bimatoprost patients. This finding should be interpreted in the context that this study was based only on prescription claims data. It is important to simplify ophthalmic medical regimen as it is more cost effective, better for the patient, and minimizes the washout effect from administering two eye medications within 5 min. Decreasing the complexity of the patients’ drug regimen may lead to increased adherence to prescribed therapy and a decreased risk of the incidence of blindness.

Introduction

Glaucoma is a pressure sensitive optic neuropathy for which there is growing powerful evidence that lowering intraocular pressure (IOP) both retards the rate and prevents further development of the disease. The National Institutes of Health’s (NIH) multi-centered Advanced Glaucoma Intervention Study (AGIS) found that consistent IOP reduction, including lowering IOP below 18 mmHg, is related to prolonged survival of visual function with minimal visual field loss in patients with more advanced glaucoma. Two other multi-centered NIH sponsored studies, the Ocular Hypertension Treatment Study (OHTS) and
the Early Manifest Glaucoma Trial (EMGT), have each independently found that every additional 1 mm of IOP lowering can translate into an approximate 10% decreased risk of glaucomatous development and progression.

Lowering IOP is currently the only accepted method of treating glaucoma. Although the American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPP) suggests that surgery, laser, or medical therapy could be used initially, most physicians prefer to initially treat glaucoma with medical therapy. For decades, beta-blockers were the most prescribed class of IOP lowering medications. Recently, in part because of increased systemic safety, greater local tolerability, and greater efficacy, prostaglandin analogs have become the preferred choice for the initial treatment of open angle glaucoma and ocular hypertension.

Regrettably, monotherapy is not always adequate to control IOP and additional adjunctive medications are required. The OHTS found that even in eyes without significant optic nerve damage as demonstrated by disk or field appearance, to achieve a long-term 20% reduction in IOP, more than 40% of individuals in the era of prostaglandin analogs need an additional medication during a relatively short 5-year period. The AGIS and Collaborative Initial Glaucoma Treatment Study (CIGTS) both found that the number of patients requiring more than one medication for IOP lowering might be closer to 80% when the disease is more advanced.

Minimizing the need for adjunctive therapy has important implications for both increasing patient adherence to prescribed therapy and decreasing the overall cost of therapy. Additionally, many adjunctive IOP lowering medications have untoward systemic side effects which can also increase medical costs. A meta-analysis of medical treatments in several therapeutic categories has demonstrated that simplifying patients’ drug regimens improves their adherence to prescribed therapy. The need for additional medications to control IOP may lead to lower adherence and result in a higher risk of disease progression especially as many glaucoma patients are already on multiple systemic medications. Additionally, there is a substantial increase in cost to both the patient and third party payer when an adjunctive medication is needed.

In this paper we have focused on the ‘adherence’ of the patient, that is, the active, voluntary collaborative involvement of the patient in a mutually acceptable course of behavior to produce the desired therapeutic result. The term compliance is more commonly used to describe a patients’ ability to take a medication.

Currently there are three prostaglandin analogs widely used in the market: bimatoprost (LUMIGAN®), latanoprost (XALATAN®), and travoprost (TRAVATAN®). If effectiveness differences exist between these three prostaglandin analogs, the need for additional medications to control IOP may also vary among these prostaglandin analogs. Some of the more commonly used adjunctive therapies in daily practice with prostaglandins at the time of this study were timolol maleate, brimonidine tartrate and timolol maleate/dorzolamide combination therapy. In this study 70% of the patients requiring adjunctive therapy used one of these drugs. Timolol maleate, an ophthalmic beta-blocker, works by decreasing aqueous humor production by blocking beta-adrenergic receptors within the ciliary body. It has reasonable safety and has been used in the treatment of glaucoma for more than 20 years. Brimonidine tartrate, an alpha-2 agonist, works by decreasing aqueous humor production and increasing uveoscleral outflow. Timolol maleate/dorzolamide combination therapy includes a carbonic anhydrase inhibitor. CAIs reduce intraocular pressure by decreasing aqueous production due to the inhibition of carbonic anhydrase in the ciliary body.

This study seeks to contrast the difference, if any, in the need for adjunctive glaucoma therapies using actual prescription data. This approach may be a suitable indicator of what happens in actual day to day situations rather than in the less realistic confines of controlled clinical trials.

Methods

The study population was identified from the Medco Health Solutions prescription claims database of approximately 65 million managed care members. The database is a large, geographically diverse administrative claims database and at the time of this study contained 3 years (2001–2003) of longitudinal pharmacy claims data. It is evenly distributed by gender (50% male and female) and represents covered lives from carriers, employers, and retirement and government plans. Approximately two-thirds of the prescriptions are generated in the retail channel comprised of 13 large pharmacies with the other one-third coming from mail order. The data were anonymized prior to analysis to assure confidentiality.

The study cohort was constructed of patients who initiated prostaglandin analog therapy (travoprost, bimatoprost, or latanoprost) between January 1, 2002 and July 31, 2002 with no prostaglandin analog use.

LUMIGAN is a registered trade name of Allergan, Inc., Irvine, CA, USA
† XALATAN is a registered trade name of Pfizer, Inc. New York, New York, USA
‡ TRAVATAN is a registered trade name of Alcon, Inc., Hunenberg, Switzerland

972 Adjunctive glaucoma therapy © 2006 LIBRAPHARM LTD – Curr Med Res Opin 2006; 22(5)
in the prior 6 months. Cohort members were also required to have 12 months of follow-up subsequent to the initial prescription. Data were available through July 31, 2003. To avoid biases due to drug exposure, patients who received less than 12 months of prostaglandin analog therapy during the study period were excluded from the study cohort. The adjunctive therapy rate for patients with shorter time frames of prostaglandin monotherapy use due to either discontinuations from glaucoma therapy or switching would not be comparable, for purposes of looking at effectiveness, to the rate for patients with at least 12 months of continuous use. Switching can be due to side effects or formulary changes. Patients were also required to be continuously pharmaceutical benefit-eligible 6 months preceding and 12 months subsequent to the initial prostaglandin analog prescription fill date.

The ‘index agent’ was defined as the first prostaglandin analog prescription filled between January 1, 2002 and July 31, 2002. Addition of an ‘adjunctive medication’ was defined as filling an IOP lowering prescription for a non-index agent with a sequential fill of the index agent followed by a refill of the non-index IOP lowering agent; as a result, patients filled a prescription for two or more bottles of the adjunctive agent. For example:

1. prostaglandin analog prescription fill (index agent);
2. initial timolol maleate prescription fill (non-index agent);
3. prostaglandin analog prescription fill (sequential fill of index agent);
4. timolol maleate (refill of non-index agent).

A subset analysis evaluated adjunctive medication use rates among ‘new’ (incident) and ‘established’ (prevalent) patients. New patients were defined as those having no record of any prescription for glaucoma medication in the 6-month prior period. Established patients were defined as those having a prescription for a glaucoma medication (excluding travoprost, bimatoprost, and latanoprost) in the 6-month prior period.

We defined time to addition of an adjunctive agent as the number of days between the initial prostaglandin analog prescription fill date and the first adjunctive agent prescription fill date during the study period. Resource utilization, although available before and after the initial prostaglandin analog prescription fill date, was outside the scope of this phase of the study and is not included.

Both t-test and chi-square were used to calculate p-values and assess significant differences between agents of interest. Additionally, due to the multiple comparisons being made using the t-test, the alpha level was adjusted for multiplicity by using the formula \((0.05/3 = 0.017)\) to determine significant differences between agents of interest. The t-test was used to calculate p-values for comparisons of mean age and average time to adding a second agent between study groups. The chi-square test was controlled for the number of new and established patients in each study group and 95% confidence intervals of the relative risk ratio were used to determine significant differences at \(p = 0.05\). All statistical and descriptive analyses were performed using SAS version 8 (Cary, North Carolina).

### Results

We identified a total of 13,171 benefit-eligible subjects who fulfilled the study criteria and were therefore included in the analysis (Table 1). In this cohort, 64% \((N = 8,381)\) of patients were initially treated with latanoprost, 20% \((N = 2,637)\) with bimatoprost, and 16% \((N = 2,153)\) with travoprost. New patients represented 79.8%, 73.9%, and 74.4% of the latanoprost, bimatoprost, and travoprost patient groups, respectively. The percentage for the latanoprost group was significantly higher than the other two groups due to the large number of patients in each group but this was not considered a clinically meaningful difference. Females comprised 52.9% of the study population and all three groups had a similar percent of females. The mean age \((\pm \text{std dev})\) for the study cohort was \(68.7 \pm 12.3\) years. Bimatoprost, travoprost, and latanoprost patients also had similar mean ages:

### Table 1. Demographic characteristics of the study cohort (N = 13,171)

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mean age (years)</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N* Mean ± std. dev.</td>
<td>Males</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>2628 68.5 ± 11.8</td>
<td>1237 46.9% 1388 52.6% 12 0.5%</td>
</tr>
<tr>
<td>Travoprost</td>
<td>2144 68.0 ± 12.3</td>
<td>1000 46.4% 1138 52.9% 15 0.7%</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>8200 69.0 ± 12.5</td>
<td>3745 44.7% 4436 52.9% 200 2.4%</td>
</tr>
<tr>
<td>Total</td>
<td>12,972 68.7 ± 12.3</td>
<td>5982 45.4% 6962 52.9% 227 1.7%</td>
</tr>
</tbody>
</table>

*199 patients with missing age were excluded from the totals*
68.5 (± 11.8) years, 68.0 (± 12.3) years, and 69.0 (± 12.5) years, respectively, with one exception. There was a significant difference between the mean age for travoprost and latanoprost patients (p = 0.0009). This difference was not considered clinically meaningful.

Twenty-eight percent of the study cohort filled a prescription for one or more adjunctive medication(s) during the study period (Table 2). Significantly more patients on latanoprost therapy filled a prescription for an adjunctive medication during the study period than either patients on travoprost (30.2% vs. 22.5%, p < 0.0001) or bimatoprost (30.2% vs. 23.2%, p < 0.0001) therapy. Therefore, for every 14 patients treated with latanoprost instead of travoprost or bimatoprost, one additional patient would be expected to need adjunctive therapy with another agent. Patients on bimatoprost filled a prescription for an adjunctive medication at a rate similar to travoprost (23.2% vs. 22.5%, p = 0.278).

For those patients that were new to glaucoma therapy, significantly more patients on latanoprost therapy filled a prescription for an adjunctive medication compared to patients on travoprost (25.0% vs. 16.8%, p < 0.0001) or bimatoprost (25.0% vs. 17.7%, p < 0.0001). New patients on bimatoprost therapy filled a prescription for an adjunctive medication at a rate similar to travoprost (17.7% vs. 16.8%, p = 0.494).

For those patients who were established on glaucoma medication, that is, they were taking a glaucoma medication prior to switching to a prostaglandin, significantly more patients on latanoprost therapy filled a prescription for an additional adjunctive medication compared to patients on travoprost (50.9% vs. 39.0%, p < 0.0001) or bimatoprost (50.9% vs. 39.0%, p < 0.0001). Established patients on bimatoprost therapy filled a prescription for an adjunctive medication at the same rate as travoprost.

In addition, patients on latanoprost therapy added an adjunctive agent on an average of 84 days after initiating prostaglandin analog therapy compared to 96 days (p-value = 0.026) for bimatoprost patients which was not significantly different at an alpha level of 0.017. A comparison of the average days for latanoprost patients and 92 days (p = 0.186) for patients on travoprost therapy was also not significantly different. The average number of days for bimatoprost and travoprost were similar (96 days vs. 92 days, p = 0.577).

**Discussion**

Many prior studies have effectively used prescription claims databases to estimate adherence to therapy and the need for monotherapy or adjunctive therapy.\(^\text{16,17}\) This approach may be preferable to studies that use efficacy data from clinical studies to model the need for adjunctive therapy based on targets for control of intraocular pressure\(^\text{16,19}\). This analysis used the Medco Health Solutions prescription claims database to examine the use of adjunctive glaucoma medications associated with bimatoprost, latanoprost, and travoprost therapy. In this study, the use of adjunctive agents was significantly higher for latanoprost patients compared to patients on travoprost or bimatoprost therapy. This finding was consistent for both new and established patients.

To our knowledge, there has not been a published, retrospective study comparing the use of adjunctive glaucoma medication by ‘new’ and ‘established’ patients starting on bimatoprost, latanoprost, and travoprost monotherapy. However, our overall findings (28%) are similar to the findings from OHTS\(^\text{3}\) that showed a high level (40%) of adjunctive medication use with prostaglandins. The results for the established patient, assumed to have experienced more disease progression, were in a higher range of 40–50% or about twice the rate for the newly diagnosed group at 17–25%. This supports findings from AGIS\(^\text{5}\) and CIGTS\(^\text{4}\) suggesting that the number of patients requiring more than one medication for IOP lowering might be closer to 70–80% when the disease is more advanced.

**Table 2. Drug utilization metrics (adjunctive medication use, time to adding the second agent)**

<table>
<thead>
<tr>
<th>Pharmacological metrics</th>
<th>Bimatoprost</th>
<th>Travoprost</th>
<th>Latanoprost</th>
<th>Travoprost vs. bimatoprost</th>
<th>Travoprost vs. latanoprost</th>
<th>Bimatoprost vs. latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent adding a second glaucoma agent</td>
<td>23.2%</td>
<td>22.5%</td>
<td>30.2%</td>
<td>0.2785</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Percent adding a second agent – new patient</td>
<td>17.7%</td>
<td>16.8%</td>
<td>25.0%</td>
<td>0.4937</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Percent adding a second agent – established patient</td>
<td>39.0%</td>
<td>39.0%</td>
<td>50.9%</td>
<td>–</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Average time to adding a second agent (days)</td>
<td>96.1</td>
<td>91.7</td>
<td>84.2</td>
<td>0.5766</td>
<td>0.1863</td>
<td>0.0261</td>
</tr>
</tbody>
</table>
Many studies have conclusively found that simplifying the patients’ daily dosing regimen is an important consideration to maintain patient adherence to the prescribed therapy. Based on a review of 76 published studies in which an electronic monitoring device was used to investigate the association between dose frequency and medication adherence, the prescribed number of daily doses was found to be inversely related to adherence. Another meta-analytic review of 168 adherence intervention studies found that simplification of the daily dosing regimen through packaging or dosing modifications produced the strongest effects on improved patient adherence.

Recent studies in the area of glaucoma also support simplification of the dosing regimen to improve patient adherence to prescribed therapy. An evidence-based review of 34 articles describing 29 original quantitative studies on non-adherence with glaucoma or ocular hypertension patients, found that patient education and fewer doses to minimize forgetfulness would be a successful strategy to enhance patient adherence. Our survey of 324 patients from four private ophthalmic practices who were taking two or more medications for glaucoma reported that the more medications that they were on, the more difficulty they had remembering to take their medications. The number of medications being used was the greatest predictor of patient adherence to prescribed therapy in the study. In this same study nearly a quarter of the patients reported waiting less than 3 min between instillation of multiple glaucoma medications and close to half reported having difficulties administering their drops. Instillation of multiple eye drops should be separated by at least 5 min to minimize the dilution effect and to maximize the full therapeutic effect of each drug.

Simplification of the drug regimen is also important when considering that these patients are dealing with more health problems than just glaucoma. Our recent study showed that over half of glaucoma patients are on multiple systemic medications ranging from antihypertensive, diabetic, arthritic, hormone replacement therapies, and other medicines. More specifically, 40% of the patients were taking three or more systemic medications per day and many of these medications required multiple doses per day. This does not include the over-the-counter medications such as H$_2$ blockers, aspirin, vitamins and, calcium.

Another consideration is that patients on multiple glaucoma medications may not refill their prescriptions promptly. Bottles of glaucoma drops come in all sizes and require frequent replacement so a higher number of medications would require more trips to the pharmacy because medications will not run out at the same time. Our study of 1748 patients on prostaglandin monotherapy who progressed to the need for adjunctive therapy, the mean refill rate for the prostaglandin therapy increased by 6.7 days after the addition of a second medication. For 23% of the patients the refill interval increased by 2 weeks. This suggests that patients do not consider taking only one of their two medications to be non-adherent since they are still taking one of their glaucoma medications.

The results of our study should be interpreted in the context of its limitations. One such limitation is the exclusion of patients on prostaglandin monotherapy for less than 12 months. This may introduce bias in that only those who tolerate prostaglandin therapy well are included in the study. There may be different patterns of adjunctive therapy use among those patients who persist on prostaglandin therapy for shorter periods of time.

Another limitation is the lack of clinical variables such as the type of glaucoma and glaucoma surgical history. The number of years on glaucoma medications is also not known and without having intraocular pressure data or other measures, the severity of disease could not be determined. However, we have attempted to assure that the study groups have similar glaucoma disease severity profiles by looking at the percent of patients that are newly diagnosed (no glaucoma prescriptions for 6 months prior to initiating prostaglandin therapy) versus those that are established patients (previous glaucoma medication use before switching to prostaglandin monotherapy). Although the percent of new patients for latanoprost (79.8%) is statistically higher than travoprost (74.4%) or bimatoprost (73.9%) due to the large number of patients in each group, these differences are not considered clinically significant. The slightly higher percent of new patients assumed to be at an earlier stage in the disease process for latanoprost suggests a lower rate of adjunctive therapy use compared to the other prostaglandins. However, it was higher and this difference remained statistically significant after controlling for the number of new and established patients.

Additionally, since this study was performed on administrative and pharmacy claims data, it does not include complete information on each patient’s medical history. The data used for this study may also contain possible coding biases and/or errors. Furthermore, the present analysis represents patients with medical and prescription benefit coverage; therefore, it may not be representative of those without benefit coverage. Finally, there was no attempt to control for age and gender in the analyses. The study groups were quite similar with regards to these two covariates which in themselves are strong predictors of a person’s health.
Conclusion

In summary, the current study compared the need for adjunctive agents by patients using prostaglandin analogs as their primary therapy. This study found that travoprost and bimatoprost patients have the lowest rate of adjunctive medication use. Therefore, a new or established patient starting on these therapies may have a better chance of avoiding a number of the problems that have been identified with the use of multiple bottles of glaucoma medications. These include patient adherence to prescribed doses, the potential washout effect from taking multiple drops, and the additional cost of adjunctive therapy to the patient and third party payer. Further studies are needed to verify our findings.

Acknowledgment

This study was funded by Alcon Research Ltd.

References

16. Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology 2005;112:863-8
19. Goldberg LD, Walt J. Cost considerations in the medical management of glaucoma in the US: estimated yearly costs and cost effectiveness of bimatoprost compared with other medications. Pharmacoeconomics 2006;24:251-64

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-3392_3, Accepted for publication: 30 March 2006
Published Online: 19 April 2006
doi:10.1185/030079906X104777