Comparison of the Efficacy and Tolerability of Xalatan® and Xalabiost (Generic Latanoprost) in Adults with Open-Angle Glaucoma or Ocular Hypertension: A Two-Center, Randomized, Crossover Trial

Masih Hashemi, MD[1] • Arezoo Miraftabi, MD[2] • Naveed Nilforoushan, MD[1]
Khalil Ghasemi Falavarjani, MD[2] • Farzad Pakdel, MD[2]
Reza Soudi, MD[3] • Shima Hatamkhani, PharmD[4]

Abstract

***Purpose*:** To compare the intraocular pressure (IOP) lowering effect and side effects of Xalatan with generic Latanoprost (Xalabiost) in adults with open-angle glaucoma or ocular hypertension

***Methods*:** This was a two-center prospective randomized, crossover clinical trial. Eligible patients with open-angle glaucoma or ocular hypertension were sequentially randomized to two parallel study groups receiving Xalatan and Xalabiost in two periods. The primary efficacy outcome was change in the mean of IOP between baseline and end of each treatment period, and secondary outcomes included differences between treatment groups in mean percent change in IOP from baseline and in proportions of patients reaching specified target mean IOP levels.

***Results*:** Nineteen patients in BX group (receiving Xalabiost in first and passing to Xalatan in second treatment period) and 22 patients in XB group (receiving Xalatan in first period and Xalabiost in second treatment period) completed both treatment periods. The mean baseline IOP was 24.9 mmHg in group XB and 25.4 mmHg in group BX (P=0.57). At the end of Xalatan treatment periods, patients experienced a 7.5±1.3 mmHg (29.8±3.6 percent) reduction in IOP compared to baseline IOP. Xalabiost treated patients had a 7.3±1.2 mmHg (29.2±3.3 percent) decrease in IOP compared to baseline IOP (P=0.084). Adverse ocular events were mild in both treatment groups.

***Conclusion*:** Both Xalatan and generic Latanoprost (Xalabiost) reduced IOP effectively after 1 month of treatment in patients with primary open-angle glaucoma or ocular hypertension, with no significant difference in efficacy and tolerability between them.

***Keywords*:** Intraocular Pressure, Latanoprost, Glaucoma

Iranian Journal of Ophthalmology 2012;24(3):11-18 © 2012 by the Iranian Society of Ophthalmology

1. Associate Professor of Ophthalmology, Eye Research Center, Rassoul Akram Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Assistant Professor of Ophthalmology, Eye Research Center, Rassoul Akram Hospital, Tehran University of Medical Sciences, Tehran, Iran
3. Ophthalmologist, Eye Research Center, Rassoul Akram Hospital, Tehran University of Medical Sciences, Tehran, Iran
4. Resident in Clinical Pharmacy, Department of Clinical Pharmacy (Pharmacotherapy), School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Received: December 31, 2011
Accepted: July 8, 2012

Correspondence to: *Reza Soudi, MD*
Ophthalmologist, Eye Research Center, Rassoul Akram Hospital, Tehran University of Medical Sciences, Tehran, Iran
Email: rezasoudi@yahoo.com

Financial disclosures: The authors have no proprietary or commercial interest in any of the materials discussed in this article. No financial support was received for this study.

Introduction

Glaucoma is one of the leading causes of blindness.[1] Most treatments for this disease are focused on reducing intraocular pressure (IOP). In open-angle glaucoma, medical therapy is considered as first line therapy.[2] Prostaglandin analogues, due to their good potency in lowering IOP and acceptable safety profile, are commonly used by ophthalmologists.[3] Latanoprost was the first drug in this class that was available since 1996 under brand name Xalatan (Pfizer, New York). It is a prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogue and reduces IOP by increasing uveoscleral outflow.[4-6]

Recently several generic forms of Latanoprost are available. Generic medications are generally less expensive because they are reverse-engineered and costly clinical trials to show their efficacy are not required for their approval. Despite the price advantage, there has been a continuous debate about the efficacy and safety of generic drugs. This study compares the efficacy and tolerability of Xalatan with a generic version of Latanoprost (Xalabiost, Bakhtar Bioshimi Pharmaceutical Co. Tehran, Iran) in adults with open-angle glaucoma or ocular hypertension in a group of Iranian patients.

Methods

This two-center prospective randomized, crossover clinical trial, was conducted according to declaration of Helsinki and approved by Ethics Committee of Tehran University of Medical Sciences.

Patients with age≥18 years and diagnosis of primary open-angle glaucoma or ocular hypertension (baseline IOP≥22 mmHg), were enrolled in this study. Exclusion criteria were a close or narrow angle at gonioscopy, history of any intraocular surgery or laser procedure in last 3 months, history of recent infectious/inflammatory ocular processes, history of known hypersensitivity to the study medications or their components (benzalkonium chloride preservative); corneal problems preventing accurate IOP measurements, contact lens usage during the study; pregnancy or nursing during the study. Patients who had advanced glaucoma and wash out was not safe including significant loss of visual field loss, best corrected visual acuity (BCVA) less than $^1/_{10}$ due to glaucoma, baseline IOP>36 mmHg, and cup-to-disc ratio of more than 0.6 in funduscopy, were also excluded. In a patient with bilateral eligible eyes, one eye was randomly selected and included in this study.

During the investigation, patients were visited four times (Figure 1). At pre-study screening visit (visit 1), patients were screened according to inclusion and exclusion criteria. Eligible patients with current glaucoma medication usage were instructed to come back after a reasonable wash out period according to the drug being used (6 weeks for β-blockers and prostaglandins, 4 days for carbonic anhydrase inhibitors, and 4 weeks for brimonidine). At the pre-study visit, all patients underwent a complete interrogation concerning the history of the patient. They had dilated fundoscopy, and visual field measurements (Humphrey 24-2 SITA standard, Humphrey Field Analyzer, Humphrey Instruments, San Leandro, CA). At each visit, patients underwent slit-lamp biomicroscopy, Goldmann applanation tonometry, and visual acuity measurements by Snellen chart.

At the second visit, the patients were sequentially randomized to two parallel study groups in 1:1 proportion: Group XB receiving Xalatan in first period and Xalabiost in second treatment period; and group BX receiving Xalabiost in first and passing to Xalatan in second treatment period. First treatment period lasted 6 weeks (visit 3) and second treatment period lasted 10 weeks (visit 4: end of treatment), with no drug-free period to increase patients safety. Ten weeks seemed to be a reasonable period for the wash-out of the first drug.[7] Patients were instructed to instill one drop every night at 9.00 PM and apply nasolacrimal occlusion for 1 minute after drug instillation.

At baseline and each subsequent visits, IOP was measured using a calibrated Goldmann applanation tonometer at 9:00 AM, 12:00 MD and 4:00 PM by a single investigator. Two measurements were performed at each time and mean of two measurements were used in statistical analysis.

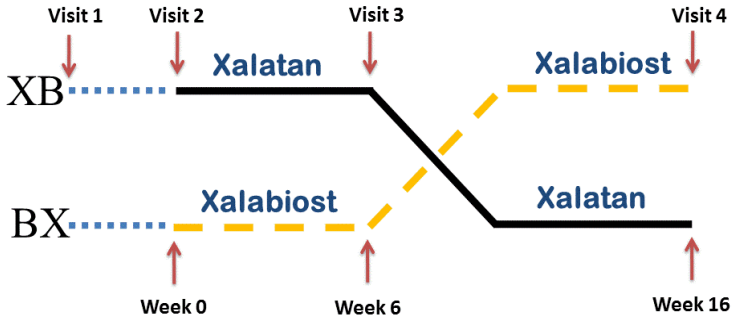


Figure1. Diagram showing study protocol

The presence and severity of bulbar conjunctival hyperemia were assessed at baseline and each subsequent visits by comparing with CCLRU standard photographs scaling conjunctival hyperemia to four grades: 0, 1, 2, and 3 (none, mild, moderate, and severe, respectively)[8,9] (Figure 1). At every visit, the patients were asked about ocular irritation/stinging and itching following drop instillation. Extent of symptoms was subjectively scaled in four grades: not at all, small, moderate, or great amount.[10] Any undesired medical event was also recorded.

With an 80% power to detect a 2 mmHg difference of mean IOP between treatment groups at a significance level of 0.05 and an estimated standard deviation of 3 mmHg, the sample size was calculated to be 35 patients.

Statistical analysis

Nominal variables were analyzed using McNemar or Wilcoxon test. Continuous variables were analyzed using a2-tailed t-test. Within-group changes in IOP from baseline to end of each treatment period were analyzed using a paired t-test. Changes in IOP between groups from the baseline to the end were analyzed using an independent t-test. A P-value of ≤0.05 was considered statistically significant. Analysis was performed using Statistical Package for Social Sciences version 18 (SPSS, Inc., Chicago, Illinois).

The primary efficacy outcome, changes in the mean of IOP measurements between baseline and end of each treatment period, were analyzed using the analysis of covariance model, with baseline IOP as the covariate and sequence of treatment as fixed factor. Secondary outcomes included differences between treatment groups in mean percent changes in IOP from baseline and in proportion of patients reaching specified target mean IOP levels.

Intent-to-treat data analysis was performed. This included every patient who had at least one valid IOP measurement at each episode of investigation, after initiation of the treatment. If a patient missed any of the three daily measurements of the IOP, the mean of the non-missing IOP values was used.

Results

Forty five patients were enrolled in this study and randomly assigned to treatment groups. Four patients (three patients from group BX and one patient from group XB) were excluded during study due to violation of study protocol. Nineteen patients in BX group and 22 patients in XB group completed both treatment periods.

Demographic data are summarized in Table 1. The two groups under investigation had no significant differences regarding age and sex of participants.

At the beginning of study, the mean baseline IOP was 24.9 mmHg (range, 22-31 mmHg) in group XB and 25.4 mmHg (range, 22-35 mmHg) in group BX (P=0.57).

At the end of the first period, the mean IOP was 17.5±1.4 mmHg in group XB and17.9±2.5 mmHg in group BX. Both treatments caused significant decrease in IOP compared to

baseline IOP (P<0.001). The mean percent reduction in IOP at the end of first period was 29.5±3.3 percent in group XB and 29.3±3.5 percent in group BX (P=0.47). The mean reduction in IOP in period 1 was 7.38±1.4 mmHg in group XB and 7.46±1.2 mmHg in group BX, the difference between the two groups was not statistically significant (P=0.49)(Figure 2).

At the end of second period (end of treatment), the mean IOP was 17.6±1.6 mmHg in group XB and17.8±2.6 mmHg in group BX. Both treatments caused significant decrease in IOP compared to the baseline IOP (P<0.001). Mean percent reduction in IOP at the end of second period 28.2±3.35 percent in group XB and 30.08±4.01 percent in group BX (P=0.22). The mean reduction in IOP in period 1 was 7.3±1.3 mmHg in group XB and 7.6±1.2 mmHg in group BX, which was not statistically significant (P=0.30).

At the end of Xalatan treatment periods (regardless of sequence), patients experienced a 7.5±1.3 mmHg (29.8±3.6 percent) reduction in IOP compared to baseline IOP. Xalabiost treated patients had a 7.3±1.2 mmHg (29.2±3.3 percent) decrease in IOP compared to baseline IOP (P=0.084).

The time that IOP was at its highest value, in both groups was at 9 AM with a mean of 18.1±1.4 for group XB and 18.7±2.4 in group BX. This also concerned to individual in each group.

Percent of patients achieving to an IOP reduction of more than 20%, 25%, 30%; and 35% in each group at the end of both treatment periods, is summarized in Figure 3. No subclass had a significant difference in reduction of IOP. The percent of patients reaching to a specific target IOP at the end of the first (Figure 4) and the second (Figure 5) period, was not evident neither.

No serious adverse event was noted during study. The most common adverse event in both groups was conjunctival hyperemia. The mean baseline conjunctival hyperemia score (in a 0 to 3 scale) was 0.31±0.4 in group XB and 0.11±0.3 in group BX. The mean conjunctival hyperemia scores at the end of Xalatan and Xalabiost periods were 1.71±0.6 and 1.80 ±0.7, respectively (P=0.36)(Table 2). Both drugs caused a significant increase in conjunctival hyperemia (P<0.001).

Eleven patients (26.8%) mentioned the stinging following instillation of Xalatan, while 14 patients (31.4%) had same symptoms following Xalabiost (P=0.41). No systemic adverse event attributable to treatment was noted.

Table1. Baseline demographic characteristics

Characteristics	Xalatan followed by Xalabiost (Group XB) No. (%)	Xalabiost followed by Xalatan (Group BX) No. (%)	P
Number of patients	22	19	
Age (mean±SD)	56.5±10.2	60±8.4	0.24
Maximum	70	75	
Minimum	38	45	
Sex			0.58
Male	10 (45.5)	7 (36.8)	
Female	12 (54.5)	12 (63.2)	
Laterality			
Right	7	6	
Left	5	4	
Bilateral	10	9	

Table 2. Common ocular adverse events in two treatment regimens

	Xalatan (n=41)	Xalabiost (n=41)	P
Ocular hyperemia			0.36
Mild	14	13	
Moderate	22	20	
Severe	4	7	
Irritation/stinging			0.42
Mild	7	8	
Moderate	3	5	
Severe	1	1	

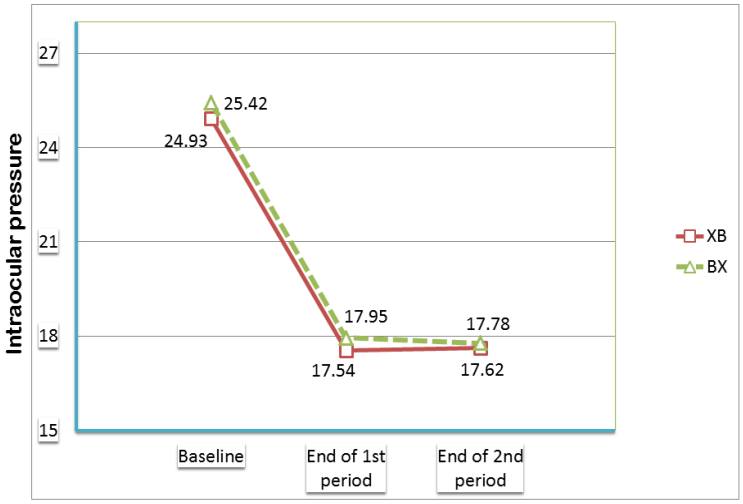


Figure 2. Mean intraocular pressure at week 6 and week 16 in two treatment groups

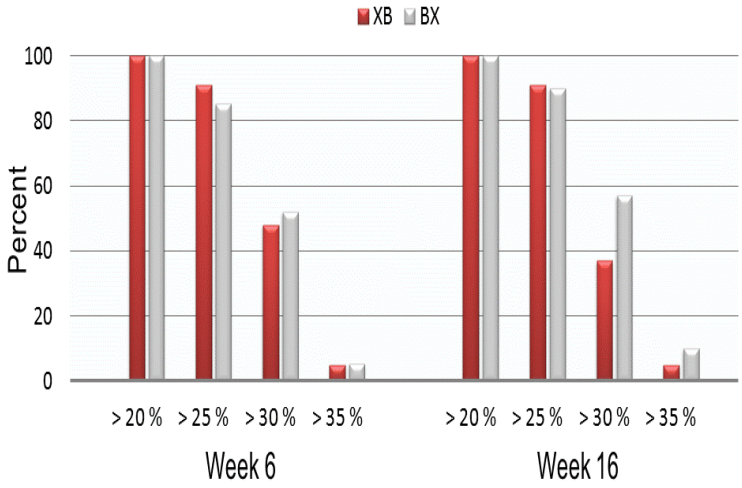
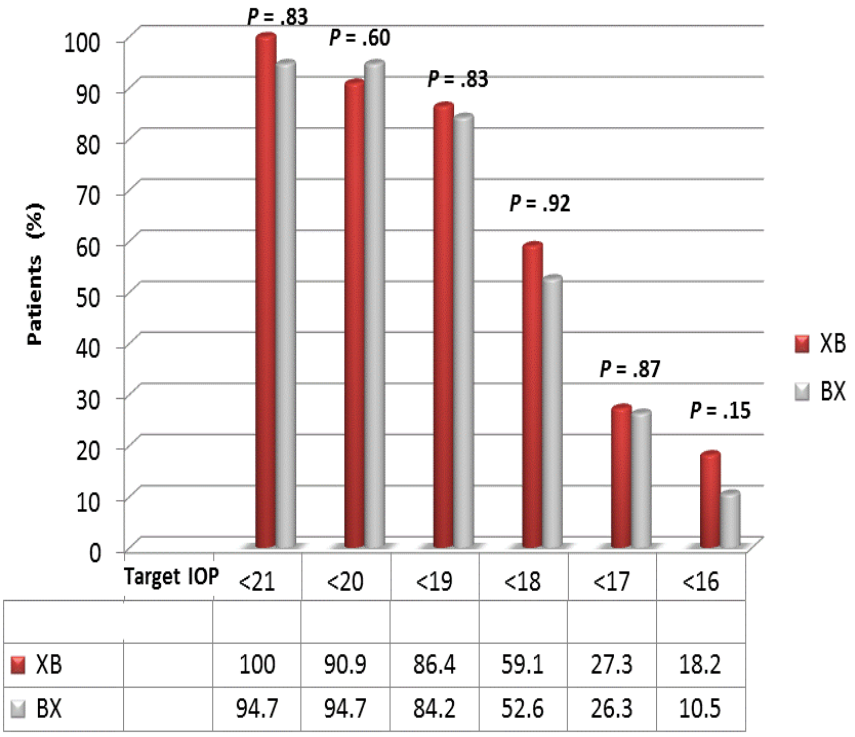
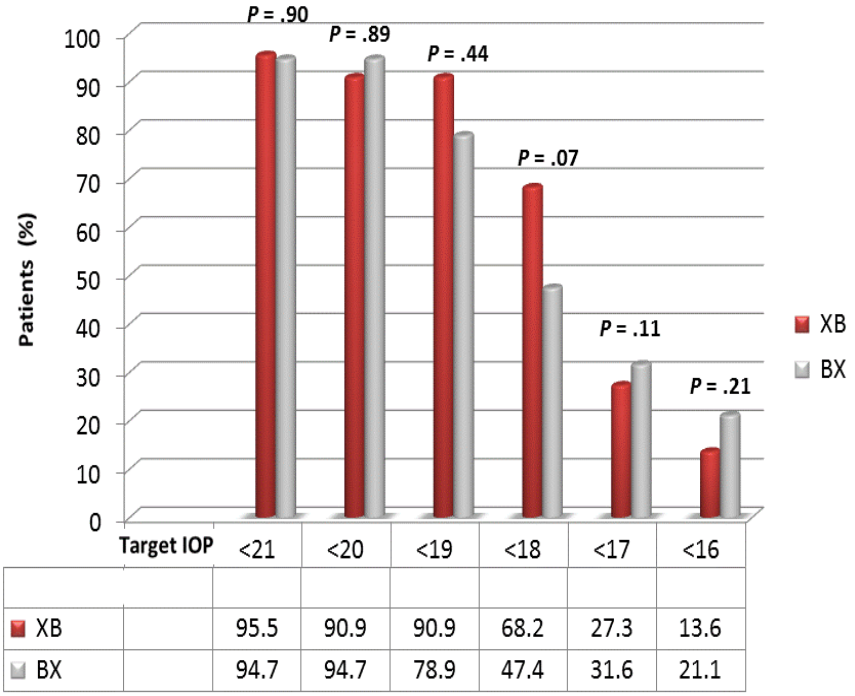


Figure 3. Percent of patients achieving to an intraocular pressure reduction of more than 20%, 25%, 30%; and 35% in each group at the end of both treatment periods



Target IOP	<21	<20	<19	<18	<17	<16
XB	100	90.9	86.4	59.1	27.3	18.2
BX	94.7	94.7	84.2	52.6	26.3	10.5

Figure 4. Percent of patients reaching to a specific target intraocular pressure at the end of first treatment period



Target IOP	<21	<20	<19	<18	<17	<16
XB	95.5	90.9	90.9	68.2	27.3	13.6
BX	94.7	94.7	78.9	47.4	31.6	21.1

Figure 5. Percent of patients reaching to a specific target intraocular pressure at the end of second treatment period

Discussion

Efficacy and safety of generic products always have been a concern to clinicians. Some studies raised the question about the concentration of active drug in generic ophthalmic drugs. Weir and his colleagues[11] compared the content of Indian ciprofloxacin eye drops and concluded that a lower concentration of active content in about 20% of samples was noted. This concern is triggered by some reports of serious complications caused by generic ophthalmic products. There are several reports of serious corneal damage and melting caused by generic topical NSAIDs.[12] In another study, Narayanaswamy and his colleagues[13] compared the efficacy and safety of Xalatan with a generic Latanoprost in 30 patients and reported higher efficacy and safety for Xalatan compared with generic Latanoprost. In contrast, Sharifipour and her colleagues[14] reported the results of a cross over study comparing efficacy and short-term safety of Xalabiost and Xalatan in 17 patients and found no significant difference between these two drugs. However, these authors proposed that a multi-center study with more patients is needed.

Absorption, elimination, and concentration of an ophthalmic drug in a target tissue cannot be measured as easily as a systemic drug. So, proving the bioequivalence of a generic ophthalmic drug with the branded one is usually based on clinical outcomes, not laboratory data.

In the other hand, in patients with chronic illnesses like glaucoma, cost of treatment - which is the main advantage of generic drugs - is a major contributor to compliance of patients to treatment regimens. But this decrease in cost should not sacrifice efficacy.[15]

The present study compared the brand name Latanoprost (Xalatan) with a generic version (Xalabiost) in patients with primary open-angle glaucoma or ocular hypertension based on clinical outcomes.

Both drugs decreased IOP significantly compared to baseline IOP. In the Xalatan-treated group the IOP reduction was 7.50±1.31 mmHg (29.75±3.64%), whereas it was 7.38±1.24 mmHg (29.28±3.32%) in the Xalabiost-treated group. The difference between treatments was not statistically significant (P=0.084). This was confirmed at the end of the period one and also at the end of period two of study. IOP did not change significantly after crossing over to Xalatan from Xalabiost in group BX and to Xalabiost from Xalatan in XB group. Overall, the percentage of responders in the Xalatan-treated group was equal to that in the Xalabiost-treated group in terms of amount of decrease in IOP.

Regarding the adverse events, both drugs were well tolerated. No systemic adverse event occurred in this study. The most common ocular adverse event was ocular hyperemia which was compatible with other studies. Both drugs caused a substantial increase in ocular hyperemia comparing to baseline, but no significant difference between two drugs was noted.

This study was limited by the relatively short treatment periods of 3 months. Also complete diurnal IOP monitoring with night-time IOP measurements was not performed, which may affect the results. Changes in iris or eyelashes which are known as Latanoprost side effects, were not assessed during this study and they are not expected to occur in short-term periods. Longer follow-up is needed to evaluate the difference in effect and safety in a longer period.

Conclusion

In conclusion, this study showed that both Xalatan and generic Latanoprost (Xalabiost) reduced IOP effectively after 1 month of treatment in patients with primary open-angle glaucoma or ocular hypertension, with no significant difference in efficacy and tolerability between them.

References

1. Jampel HD, Bacharach J, Sheu WP, et al. Randomized clinical trial of Latanoprost and unoprostone in patients with elevated intraocular pressure. Am J Ophthalmol 2002;134(6):863-71.

2. Grant WM, Burke JF Jr. Why do some people go blind from glaucoma? Ophthalmology 1982;89(9):991-8.
3. Konstas AG, Maltezos AC, Gandi S, et al. Comparison of 24-hour intraocular pressure reduction with two dosing regimens of latanoprost and timolol maleate in patients with primary open-angle glaucoma. Am J Ophthalmol 1999;128(1):15-20.
4. Aung T, Chew PT, Yip CC, et al. A randomized double-masked crossover study comparing latanoprost 0.005% with unoprostone 0.12% in patients with primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol 2001;131(5):636-42.
5. DuBiner HB, Mroz M, Shapiro AM, et al. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. Clin Ther 2001;23(12):1969-83.
6. DuBiner H, Cooke D, Dirks M, et al. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: a 30-day comparison with latanoprost. Surv Ophthalmol 2001;45 Suppl 4:S353-60.
7. Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.005%. Am J Ophthalmol 2001;131(6):798-9.
8. Parrish RK, Palmberg P, Sheu WP; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003;135(5):688-703.
9. Murphy PJ, Lau JS, Sim MM, Woods RL. How red is a white eye? Clinical grading of normal conjunctival hyperaemia. Eye (Lond). 2007;21(5):633-8.
10. García-Sánchez J, Rouland JF, Spiegel D, et al. A comparison of the fixed combination of latanoprost and timolol with the unfixed combination of brimonidine and timolol in patients with elevated intraocular pressure. A six month, evaluator masked, multicentre study in Europe. Br J Ophthalmol 2004;88(7):877-83.
11. Weir RE, Zaidi FH, Charteris DG, et al. Variability in the content of Indian generic ciprofloxacin eye drops. Br J Ophthalmol 2005;89(9):1094-6.
12. Fiscella RG, Gaynes BI, Jensen M. Equivalence of generic and brand-name ophthalmic products. Am J Health Syst Pharm 2001;58(7):616-7.
13. Narayanaswamy A, Neog A, Baskaran M, et al. A randomized, crossover, open label pilot study to evaluate the efficacy and safety of Xalatan in comparison with generic Latanoprost (Latoprost) in subjects with primary open angle glaucoma or ocular hypertension. Indian J Ophthalmol 2007;55(2):127-31.
14. Sharifipour F, Pakravan M, Yazdani S, et al. [Comparison of efficacy and safety of Xalatan(R) with Generic Latanoprost (Xalabiost) in patients with glaucoma: a pilot study]. Bina J Ophthalmol 2010;15(2):105-10.
15. Piette JD, Heisler M, Wagner TH. Cost-related medication underuse: do patients with chronic illnesses tell their doctors? Arch Intern Med 2004;164(16):1749-55.