Latanoprost PF Vs. Bimatoprost PF: Which treats better the ocular surface? A case series.

Introduction

Glaucoma is defined as a group of neuropathies that result in progressive optic nerve atrophy, with characteristic changes in the optic head and progressive visual fields defects. It is also the leading cause of global irreversible blindness, and the number of glaucoma patients aged over 40 years is estimated to increase to 111.8 million in 2040 worldwide [1]. The main strategy for treating glaucoma is to control the intraocular pressure (IOP) by administering antiglaucoma eye drops for a prolonged and sometimes lifelong period of time. The most effective drugs for increasing outflow of aqueous humor, and consequently reducing intraocular pressure, are the $PGF_{2\alpha}$ analogs [2,3], which consist the primary intervention [3]. A considerable number of glaucoma patients experience ocular surface disease symptoms which can affect the quality of life and adherence to therapy [4-6].

Evaluating the ocular surface in patients with glaucoma is a very important procedure for maintaining a good quality of life and a good visual function. Although a number of tests can be performed in order to evaluate the condition of the tear film, both Schirmer's test and tear break-up time (TBUT) often do not correlate with the clinical symptoms reported by the patient. Especially, the Schirmer test is unrepeatable due to the reflex tear produced by its irritating nature [7,8] and TBUT can be unreliable because of the use of topical anesthetic agents which destabilize the tear film and lead to an artificially accelerated TBUT [8,9]. A novel approach of evaluating ocular surface disease has been reported lately by Chotikavanich et al. [10]. They have shown that the levels of the molecule matrix metalloproteinase-9 (MMP-9) are elevated in patients with severe OSD, Meibomian gland dysfunction, Sjogren's syndrome and glaucoma [10]. MMPs are proteolytic enzymes produced by stressed ocular surface and grandular epithelial cells, as well as by the inflammatory cells that infiltrate those tissues [10]. MMPs play a vital role in wound healing and inflammation [11,12]. Among MMPs, MMP-9 has been found to be of central importance in cleaving epithelial basement membrane components and tight junction proteins that maintain corneal epithelial barrier function [13-15]. MMP-9 belongs to the gelatinase group of metalloproteinases that degrade denatured collagen; native collagens type IV, V and VII; and elastin. The normal MMP-9 level in human tears is low (3-40 ng/ml) [16].

Elevated MMP-9 levels have been found in the tears of patients with OSD [10,17,18], advanced keratoconus, fungal inflammation and pterygium.

Recently, an MMP-9 point-of-care device (InflammaDry, Rapid Pathogen Screening Inc. Sarasota, FL, USA) has demonstrated good agreement for confirming OSD. Patients with glaucoma often exhibit OSD, the incidence and severity of which are underestimated [19]. InflammaDry is a rapid test that detects elevated MMP-9 levels in tear fluid samples taken from the lower eyelid's palpebral conjunctiva. It uses direct sampling microfiltration technology. Results are obtained in 10 minutes with high sensitivity (85%) and specificity (94%) [20]. A positive result indicates that the tear MMP-9 levels are >40ng/ml [16].

The aim of the current case series study is to compare preservative free (PF) Latanoprost and preservative free (PF) Bimatoprost in promoting OSD in glaucoma patients. As mentioned above it is well described that BAK preserved glaucoma eye drops promote OSD in higher rates than the preservative free eye drops. To the best of our knowledge this is the first attempt in literature to compare two of the most prescribed and first line treatment preservative free eye drops (Latanoprost PF and Bimatoprost PF). Additionally, we describe a simple way to reverse the OSD induced by the examined preservative free glaucoma eye drops.

Cases presentation with illustrations and figures

We examined 16 cases (16 eyes) in total. 10 cases were included in the Primary Open Angle Glaucoma (POAG) group and 6 cases were included in the control group. The POAG subgroup was further divided in 2 sub-groups. Especially, 4 patients had been receiving only Latanoprost PF (50 μg/mL) for at least 6 months, as glaucoma monotherapy and 6 patients only Bimatoprost PF (0.3 mg/mL) as monotherapy for the same period of time. The control group cases did not instill any kind of eye drops in their eyes. The exclusion criteria for both groups were as follows: 1) active inflammation or infection such as conjunctivitis, keratitis, uveitis 2) Sjogren syndrome 3) a recent history of ocular surgery <6 months, 4) Meibomian gland dysfunction, 5) recent trauma, 6) contact lens use, 7) allergy, 8) diabetes mellitus.

Cases' demographics, the results of the InflammaDry test as well as the Schirmer test and the TBUT are summarized in table 1. A very interesting finding is that none of the cases receiving Latanoprost PF revealed a positive InflammaDry test, on the contrary 5 out of the 6 cases (83,3%) receiving Bimatoprost PF as glaucoma monotherapy, revealed a positive InflammaDry test. This difference was statistically significant (p value= 0,027) after performing

Pearson's chi-square test. In the control group 2 out of 6 cases (33.3%), revealed InflammaDry test positivity. The statistical analysis did not reveal any other statistically significant correlation. We describe more extensively one illustrative case (case 13).

Table 1: Demographics of the cases examined. InflammaDry test results, Schirmer test, TBUT.

Case	Sex	Age	Medication	Inflammadry	Schirmer	TBUT
1	F	72	Control	Positive	9	8
2	F	52	Control	Negative	12	20
3	F	48	Control	Positive	6	23
4	F	65	Control	Negative	12	6
5	F	48	Control	Negative	4	7
6	F	66	Control	Negative	5	17
7	F	84	Latanoprost PF	Negative	11	30
8	F	66	Latanoprost PF	Negative	10	18
9	F	75	Latanoprost PF	Negative	17	12
10	F	62	Latanoprost PF	Negative	12	9
11	M	76	Bimatoprost PF	Positive	13	13
12	F	74	Bimatoprost PF	Positive	22	15
13	M	65	Bimatoprost PF	Positive	7	10
14	F	73	Bimatoprost PF	Positive	12	13
15	F	72	Bimatoprost PF	Negative	20	11
16	M	50	Bimatoprost PF	Positive	5	10

Case 13

From the Bimatoprost PF group we chose the patient with the most severe OSD symptoms. Patient No 13 is a 65 years old man, who is instilling Bimatoprost PF for more than 6 months in both eyes for POAG. He had been complaining for redness, burning sensation, watery, itchy and gritty eyes. That patient does not refer any other ocular pathology. In figure 1 we present his right eye during presentation as well as the positive InflammaDry test (Figure 2) performed at the same eye, the same day.

We immediately prescribed natural tears with trehalose 3% and sodium hyaluronate 0.15% in a preservative-free formulation 4 times daily in both eyes. We re-examined the patient 3 months after receiving the natural tears prescribed as well as the Bimatoprost PF eye drops. The patient claimed that he felt much better and the symptoms have been almost eliminated. As shown in Figure 3, his right eye is in a much better condition, less red and the InflammaDry test was negative (Figure 4).

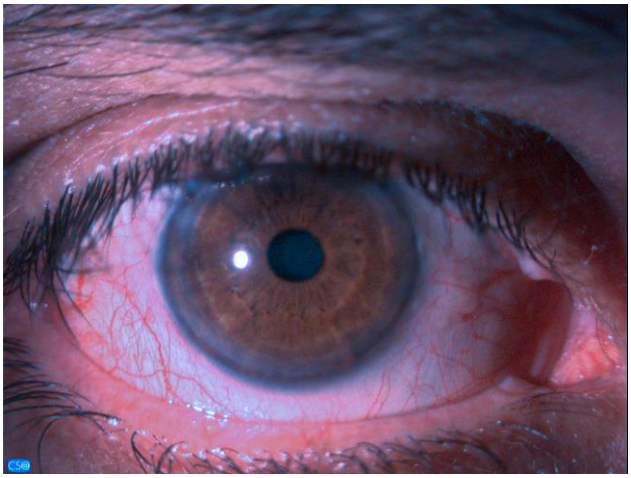

Figure 1: Right eye receiving Bimatoprost PF eye drops.

Figure 2: InflammaDry positive test performed in the right eye of the patient in figure 1.

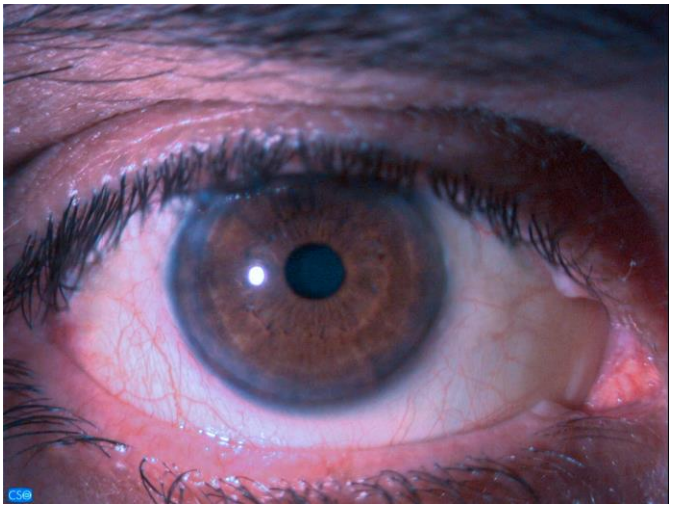

Figure 3: Right eye 3 months after receiving natural tears with trehalose 3% and sodium hyaluronate 0.15%.

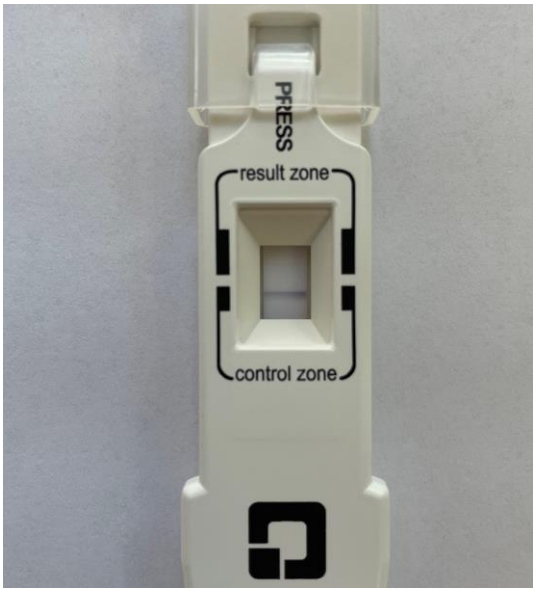

Figure 4: InflammaDry negative test performed in the right eye of the patient in figure 3.

Discussion

The major goals of glaucoma treatment include not only the IOP control but also the good quality of life of the patient. Subsequently, the management of the coexisting OSD in glaucoma patients is really important in order to maintain a good quality of life. Batra et al. have demonstrated that controlling OSD, resulted not only in the improvement of the OSD, but also in better IOP control [21]. Non adherence to glaucoma eye drops is a significant barrier to the successful treatment of glaucoma.

Tear film dysfunction in glaucoma patients is mainly a result of the chronic use of preserved eye drops. The adverse effect of the preservative BAK has been well documented [22]. Additionally, Walimbe et al. have demonstrated that switching from a BAK-containing formulation to a preservative-free topical medication led to TBUT improvement [23].

The ocular surface disease symptoms is the second most common reason for switching medication, after low efficacy, which can lead to treatment failure and glaucoma progression [4]. Most eye drops contain a preservative in addition to the active substance. Benzalkonium chloride (BAK) is the most frequently used preservative and studies have shown that BAK can affect the ocular surface by inducing squamous metaplasia of the conjunctival epithelium and by inducing proinflammatory cytokines along with a decrease in the number of goblet cells [24,25].

The most frequently reported symptoms of ocular surface disease include burning and watery eyes, redness and blurred vision. In order to avoid the BAK induced symptoms, we can administer preservative free prostaglandin analogs, such as Latanoprost UD and Bimatoprost UD, which show similar efficacy and better tolerability [26].

MMP-9 possesses a central role in the ocular inflammation procedure. MMP-9 activates the precursor IL-1β and latent TGF-B1 into their active forms [27,28]. As mentioned above, InflammaDry is a simple, inexpensive and efficient test with high sensitivity and specificity, to detect MMP-9 levels in tears samples. Zaleska-Zmijewska et al. reported that clinically significant MPP-9 levels (>40ng/mL) were detected in the tear film from 46.7% of patients treated with BAK-containing medication. In contrast only 16.7% of patients treated with preservative-free medication or untreated individuals demonstrated similar MMP-9 levels [29]. Kim et al. compared 67 patients with POAG, receiving topical preserved medication, with 47 healthy control subjects. MMP-9 overexpression was observed in 71.6% of POAG group, whereas only 31.9% of control group showed MMP-9 overexpression. Additionally, the POAG group was further subdivided according to the number of glaucoma medications received, 1, 2 or 3 bottles. The MMP-9 positivity to those sub groups was 25.0%, 40.9% and 61.9% respectively. That finding suggests that the more preserved topical medications a patient receives, the higher possibility of ocular inflammation occur [30].

Prostaglandin analogs are the first line treatment in patients with glaucoma and they are available in preserved as well as preservative free formulas with the same efficacy [26]. Our case series study is the first of our knowledge that focuses only on preservative free prostaglandin analogs (Latanoprost and Bimatoprost). The purpose of our study was to examine whether or not the above PF prostaglandin analogs induce OSD. For that purpose we performed the InflammaDry test in all glaucoma patients and control subjects, as well as Schirmer test and TBUT test. We noticed higher rates of MMP-9 overexpression in glaucoma patients receiving Bimatoprost PF medication (83.3%). On the contrary none of the glaucoma patients receiving Latanoprost PF showed MMP-9 overexpression. The difference between those two subgroups was statistically significant ($p=0.027$). The control subjects revealed a low percentage of MMP-9 overexpression (33.3%). The statistical analysis did not reveal any statistically significant correlations amongst the other measurements (Schirmer test, TBUT). The main restriction factor of our case series study is the limited number of the cases examined. We are currently expanding the number of patients and control subjects examines, so as to reveal

any potential statistically significant correlations and export useful conclusions concerning OSD that can modify the clinical practice. As mentioned above, the preservative BAK is a well-known inducing factor of OSD, but we should probably examine whether prostaglandin analogs induce OSD too. In every day clinical practice we avoid to prescribe prostaglandin analogs in neovascular glaucoma [31] or uveitic glaucoma [32], situations with intraocular inflammation. However, further experiments are needed in order to examine if prostaglandin analogs promote OSD.

The next step in our present study was to provide patients a simple way to reverse ocular inflammation without altering the medication. For that purpose we selected the patient from the Bimatoprost PF group with the worst OSD symptoms referred. We administered to that male glaucoma patient, artificial tears with trehalose 3% and sodium hyaluronate 0.15% in a preservative-free formulation 4 times daily in both eyes, in parallel with Bimatoprost PF. As shown in figures 3 and 4, his symptoms were improved and the expression of MMP-9 was reduced in normal levels.

Conclusion

The current case series study is the first that compares two of the most prescribed and first line treatment, preservative free prostaglandin analogs (Latanoprost PF Vs. Bimatoprost PF). Latanoprost PF (50 μg/mL) treats better than Bimatoprost PF (0.3 mg/mL) the ocular surface as it does not induce the overexpression of the MMP-9 inflammatory molecule. Additionally, the administration of natural tears with trehalose 3% and sodium hyaluronate 0.15% can reverse the ocular inflammation by reducing the expression levels of MMP-9 and generally resolve the symptoms of ocular surface disease. The current study has to be enriched with more patients so as to examine whether more statistically significant correlations can be exported.

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