The Role of Preservative-free Therapies in the Treatment of Glaucoma

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Abstract
The satellite symposium ‘Role of Preservative-free Therapies in the Treatment of Glaucoma’ at the 2013 annual meeting of the European Society of Ophthalmology in Copenhagen included presentations from four leaders in the field of glaucoma treatment. The first of these stressed that among patients with glaucoma, 20–30 % have severe ocular surface disease (OSD). The risk of OSD is significantly increased by preservatives such as benzalkonium chloride in topical glaucoma medications. To reduce this risk, preservative-free (PF) treatments have been developed. One such treatment, PF-tafluprost has proved effective in ‘real-world’ use in controlling intraocular pressure (IOP) and patients may benefit when switched from other treatments. When using these treatments it is important to recognise that continuous monitoring in glaucoma is vital to fully assess the IOP profile and determine the risk of disease progression. It is also important that advances in glaucoma treatment are reflected in current recommendations. Since 1998, the European Glaucoma Society has published guidelines that aim to improve definitions, diagnosis, treatment goals and practice in this disease. These have been regularly updated and constitute the consensus on best practice in glaucoma including recommendations on use of PF medications and patient management at all stages of the disease.

Keywords
Glaucoma, ocular surface disease, preservative-free (PF) therapies, PF-tafluprost, glaucoma guidelines

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Prevalence and Risk Factors for Ocular Surface Disease among Glaucoma Patients

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Ocular surface disease (OSD) is common in glaucoma and its incidence is markedly increased with the use of medications applied as eye drops to the eye. Various observational studies conducted in recent years in Europe and the US have shown a consistent prevalence of OSD in glaucoma of approximately 50 % (range: 40 %–60 %)1–5 with 27 % of patients suffering from severe OSD (see Figure 1).

These studies have also shown that patients using medications containing preservatives, particularly benzalkonium chloride (BAK), are significantly more likely to have OSD than those using preservative-free (PF) medications and that OSD is positively correlated with the number of medications used.1,3–7 This association was emphasised in one study on 101 patients in the US showing that each additional BAK-containing eye drop administered was associated with approximately twofold higher odds of abnormal results on the lissamine green staining test.4

A recent study of 516 patients with glaucoma in France found that the disease could be divided into three groupings in terms of OSD: Group A who were considered normal (score 1–4, 49 %), Group B who were mild to moderate (score 5–10, 30 %) and Group C who were severe (score 11–30, 21 %).1 The proportions of Group B and C patients were found to be substantially higher in groups who had received two or three medications compared with those who had received only one and
this correlation was significant (p<0.0001) (see Figure 2). In addition, increasing proportions of patients in groups A, B and C had changed their medication due to ocular surface concerns (24.0 %, 46.1 % and 70.4 %, respectively, 40 % in total).

A multicentre cross-sectional epidemiological study in four European countries that surveyed 9,658 patients with glaucoma over a 6-year period found that symptoms including a stinging or burning, a dry eye sensation, tearing, anterior blepharitis, conjunctival follicles and superficial punctate keratitis were all significantly more frequent among patients receiving preservative-containing than PF medication.

It should be stressed that allergies and toxic effects of medications are always possible and can occur in a delayed manner in patients who previously appeared to tolerate them. Damage induced by BAK or other preservatives at the ocular surface can appear as allergic or toxic effects and often arises when the eye is sensitised by the repeated application of preservatives during long-term use.11 Such allergic reactions to preservatives often manifest as a conjunctivitis-type condition that may consist of simple hyperaemia of the conjunctiva or papillary conjunctivitis, with or without eczema of the eyelids.

During the early stages of OSD, notable symptoms may not be present but important inflammatory process are underway that cause increasing damage. Such processes can also be triggered during long-term treatment of glaucoma. A study of 69 patients with glaucoma in France who were treated with preserved and unpreserved beta-blockers (0.5 % timolol and other medications) and 27 normal individuals, found that various inflammatory and degenerative markers were over-expressed in conjunctival cells in glaucoma patients compared with normal individuals.12–14 Similarly, increased expression was seen in patients who had received multiple treatments or preserved medications. These markers included human leukocyte antigen DR (HLA-DR), interleukin 6 (IL-6), IL-8, IL-10, chemokine receptor type 4 (CCR4), CCR5, chemokine (C-C motif) ligand 2 (CCL2 or monocyte chemotactic protein-1 (CCL2/MCP-1), extracellular matrix metalloproteinase inducer (EMMPRIN) and the chemokine fractalkine. The conjunctival cells in glaucoma patients also showed increased infiltration by inflammatory cells, increased fibroblast density and decreased goblet cell density.15 A survey of 581 glaucoma patients found that the symptoms of OSD are responsible for substantial decreases in quality of life (QoL).11 Responses showed that burning, itchy eyes, dry eyes and hyperaemia reduced QoL by between 15 and 20 %.

Receiving preserved glaucoma medications is also associated with poor surgical outcomes. Several studies have shown increased infiltration by inflammatory cells related to glaucoma medication and this was correlated with filtration surgery failure.16–18 Another study showed a positive correlation between successful surgery and low HLA-DR/high mucin-5AC (MUC 5AC).19 The duration of use of topical medication has also been correlated with increasing levels of MCP-1, which is associated with increased corneal scarring and poorer surgical outcomes.20 The recent Preservative Exposure and Surgical Outcomes in Glaucoma Patients (PESO) study investigated 128 patients with glaucoma and showed that preoperative exposure to BAK significantly increased the risk of surgical failure (p=0.032).18

In OSD, therefore, symptoms such as chronic conjunctivitis, allergy, dry eye, blepharitis and toxic keratitis do not give the complete picture. It is important to consider that low-grade subclinical inflammation, exacerbated by medications with preservatives, can cause continuous cytokine release, goblet cell loss and fibroblast stimulation that result in damage and can affect surgical and IOP outcomes. This significance of the inflammation is often underestimated and the resultant cytokines, chemokines and matrix metalloproteinases may influence glaucoma surgery, the efficacy of medications or trabecular meshwork function.

Patients who may benefit from PF treatment include those with OSD that is independent of glaucoma, such as those with moderate to severe dry eye symptoms (e.g. keratoconjunctivitis sicca), patients with moderate to severe blepharitis or those with allergic conjunctivitis or rosacea. Patients with OSD caused by glaucoma treatment, especially those who have had two or more medications, will also benefit and this group includes patients who are expected to receive long-term topical treatment for glaucoma and patients who may need glaucoma surgery (e.g. taking three to four drugs but IOP still not controlled).

Twenty to thirty per cent of glaucoma patients suffer from severe ocular surface disease. Forty per cent of glaucoma patients have had a change of their medication due to ocular surface concerns. Preoperative exposure to BAK significantly increases the risk of surgical failure.

**Figure 1: Prevalence of Ocular Surface Disease in Glaucoma Patients**

Each additional benzalkonium chloride-containing eye drop was associated with approximately twofold higher odds of abnormal results on the lissamine green staining test. Source: Leung et al., 2008.

**Figure 2: Effect of Mono-, Bi- and Tritherapy on Disease Severity in Glaucoma**

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There are now several PF medications available for the treatment of glaucoma, including the betablocker, timolol maleate, the carbonic anhydrase inhibitor (CAI) dorzolamide hydrochloride, a timolol and dorzolamide combination (Cosopt) and the prostaglandin analogue tafluprost (Taflotan/Saflutan/Zioptan). Among glaucoma treatments, the prostaglandins are currently the first-line choice in that they have a stronger IOP-lowering effect and fewer systemic side effects than other treatments.\(^\text{24}\) Each of the prostaglandins has a different binding profile from the FP and EP receptors and as a result, has differing effects on blood vessels, blood flow and hyperaemia.\(^\text{25,26}\) Consequently, individual patients show varying responses to the range of prostaglandins that are available and changing these drugs can have an effect on efficacy and/or tolerability.

As stated above, many of the topical treatments for glaucoma contain preservatives, particularly BAK, which cause irritation and inflammation that often causes poor compliance with worsening disease symptoms and OSD.\(^\text{24,25}\) PF-tafluprost 0.0015 % (Taflotan/Saflutan Ziopant) was developed to minimise these effects by being PF while being highly effective in the reduction of elevated IOP in open angle glaucoma and ocular hypertension. PF-tafluprost can be used as monotherapy in patients who would benefit from PF eye drops or are insufficiently responsive to first-line therapy or are intolerant or contraindicated to first-line therapy.\(^\text{27,28}\) It can also be used in combination with beta-blockers. The efficacy and safety of PF-tafluprost in glaucoma treatment has been shown in a series of phase II and III trials and its non-inferiority to latanoprost has also been reported.\(^\text{29,30}\) These studies showed that the preservative is not needed to provide drug efficacy. PF-tafluprost was approved for use in glaucoma in European countries in 2008 and by the US Food and Drug Administration (FDA) in 2012.\(^\text{20}\) It is useful therefore to also consider ‘real-world’ clinical experience with this drug since its introduction.

A European open-label observational study recruited 544 patients at 132 centres who had poor IOP control and/or poor local tolerance of their medication and had received prior treatment with PF-tafluprost.\(^\text{25}\) Patients were either new to therapy (n=45), were receiving monotherapy (n=360) or were receiving combination therapy (n=139). Patients (mean age 65.5 years, male/female: 205/339, had glaucoma for a mean 6.5 years) were then either treated with PF-tafluprost as their primary therapy, switched to PF-tafluprost monotherapy or PF-tafluprost as part of their combination therapy for a 12-week duration. The reasons for this switch to PF-tafluprost included: insufficient lowering of IOP, target pressure not achieved (54.4 %), ocular symptoms (irritation, burning, etc.) (17.3 %) and objective clinical signs (13.4 %). Mean IOP was lowered from 19.4 mmHg at baseline to 15.3 mmHg at 12 weeks (p<0.001). Similarly, significant reductions in mean IOP were shown in the subgroups of patients who were treatment-naive or had previously received betablocker-monotherapy, prostaglandin/prostaglandin-potency and CAI monotherapy. Switching patients from PF betablocker therapy or PF carbonic anhydrase treatment to PF-tafluprost also produced significant reductions in IOP (p<0.001 and p<0.05, respectively). In addition, PF-tafluprost produced reductions in mild, moderate and severe hyperaemia and blepharitis during treatment and reduced tear break-up time (TIBUT). The major reasons for terminating PF-tafluprost therapy were efficacy (3.1 %), tolerability (2.6 %) and adverse events (1.5 %). Overall PF-tafluprost was effective, comfortable and safe, and it improved subjective symptoms and clinical signs significantly compared with previously used medications in the observed glaucoma patients.
A later subgroup analysis of the European open-label study revealed some interesting insights on the 118 patients who had previously received prostaglandin monotherapy (latanoprost [57.6 %], travoprost [27.1 %] and bimatoprost [15.3 %]) prior to switching to PF-tafluprost.\(^6\) Overall, these patients showed a reduction in IOP of 1.4 mmHg (–8.7 %) (p<0.001 versus baseline) (see Figure 3). In this patient subgroup, the most frequent reasons for changing therapy were ocular signs and symptoms (61.0 %), insufficient lowering of IOP (20.3 %), contraindications (5.9 %) and systemic intolerance (5.1 %). After previous prostaglandin treatment in this group, the symptoms of burning, foreign body sensation, itching, irritation, stinging, tearing and dryness were more frequent than in the entire patient population, occurring in approximately 9–20 % versus 7–17 % or patients, respectively, whereas after subsequent PF-tafluprost treatment they occurred in 0–10 % of patients. In addition, hyperaemia was reduced from 64.5 % to 13.7 % (see Figure 4). The main reasons for termination of PF-tafluprost were efficacy (2.5 %), patient preference (1.7 %) or hyperaemia (1.7 %), but 89.8 % of patients remained on this therapy.

PF-tafluprost lowered IOP effectively. PF-tafluprost may benefit glaucoma patients with objective signs and subjective symptoms. Conjunctival hyperaemia was reduced during PF-tafluprost treatment compared with prior treatment with preserved PGA.

New Perspectives on 24-hour Intraocular Pressure Management

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When monitoring patients with glaucoma it is important to be aware that it is a 24-hour disease: IOP can vary widely during this period and a single IOP reading will fail to capture most of IOP-related pathology.\(^3,\)\(^7\) IOP in glaucoma is often monitored just once daily. This single IOP reading provides evidence for only 1 out of 1,440 minutes, that is, 0.0007 % of the day. It is therefore vital to assess how well drug treatments control elevated IOP at all times in order to determine how suitable they are in treating any individual patient.\(^3,\)\(^7\) In addition, tolerability, resulting from the maintenance of good ocular surface health and reduction in hyperaemia, are vital to the success of any medication in glaucoma.\(^3,\)\(^7\) In recent years, various clinical studies have demonstrated the efficacy and tolerability of PF-tafluprost versus other treatments in glaucoma and the absence of preservatives improved ocular surface health, but these studies used single point IOP determinations.\(^1,\)\(^2,\)\(^7\) Consequently, we conducted the first study that monitored the 24-hour lowering effects of PF-tafluprost and a comparator (latanoprost). This was a prospective, observational, single-masked study that included 38 patients (52.6 % female, mean age: 66.7 years) with primary open angle glaucoma. The untreated baseline IOP was 24–33 mmHg. Three months after starting treatment with either prostaglandin, IOP was monitored using Goldmann applanation tonometry\(^4\) (sitting IOP at 10:00, 14:00, 18:00, 22:00 and Perkins tonometry\(^5\) (supine IOP at 02:00 and 06:00).

IOP during treatment with either latanoprost or PF-tafluprost was markedly reduced compared with baseline (29.3 % and 28.5 %, respectively) and the IOP profiles of the two drugs were almost identical during the 24-hour monitoring period (mean difference 0.1 mmHg) (see Figure 5). The study showed that obtaining the efficacy profile of PF-tafluprost would not have been possible without 24-hour monitoring and that this approach revealed the true IOP-lowering characteristics. PF-tafluprost lowered IOP to a greater extent at night whereas latanoprost reduced it to a greater extent during the day. In addition, latanoprost produced a larger 24-hour trough IOP reduction but PF-tafluprost provided a significantly lower 24-hour fluctuation and such fluctuation is considered to be a risk factor for glaucoma progression.\(^2,\)\(^5\) PF-tafluprost was generally better tolerated: 22 patients experienced adverse events on latanoprost and 14 on PF-tafluprost. The results of this study concur with the findings of a meta-analysis of 11 previous studies (386 patients) that compared the three previously available prostaglandin analogues in the treatment of glaucoma (bimatoprost, travoprost and latanoprost) in which IOP was reduced by 24–29 %.\(^3,\)\(^7\) The differences in day/night lowering of PF-tafluprost versus latanoprost were also similar to those of a study in 30 healthy individuals in Japan in which the mean difference in IOP between the two drugs was 0.1 mmHg.\(^3,\)\(^7\) The results were also consistent with previous experience showing good tolerability for PF-tafluprost.\(^7\) In this study, therefore, PF-tafluprost showed similar efficacy but improved tolerability compared with latanoprost. PF-tafluprost will also be more suitable for use in combinations of medications in which maintaining ocular surface health is a concern.

When treating open angle glaucoma and ocular hypertension it is necessary to consider both 24-hour efficacy and tolerability and avoid exposure to BAK wherever possible. The cross-over trial data from 38 patients with glaucoma reported above showed that 24-hour efficacy of PF-tafluprost is similar to latanoprost but has improved tolerability suggesting it can be considered as first choice in glaucoma therapy. PF-tafluprost provided a significantly lower 24-hour fluctuation, which may be important in prevention of glaucoma progression.
Glaucoma is a potentially blinding disease affecting up to 10% of the population in some countries, making it the second largest cause of blindness worldwide. It is a serious healthcare need. However, large variations in diagnostic definitions, treatment patterns, and goals of treatments and resources available for the care of patients with glaucoma exist. In the mid-1990s, it was considered that there were substantial potential benefits to be gained from formulating diagnostic definitions, devising agreed treatment guidelines, and performing outcome analyses in glaucoma. This would help to make the treatment more consistent and evidence-based. In 1996, the European Glaucoma Society (EGS) assembled an international panel to discuss and draft the guidelines. These guidelines were required to be dated, they should gather feedback on QoL (as assessed by patients and physicians) and costs and should be periodically reviewed (every 5 years). The first edition of the guidelines was published in 1998 with the following mission statement:

"Preservation of visual function adequate to the individual needs with minimal or no side effects for the expected lifetime of the patient, without any disruption of his/her normal activities at a sustainable cost."

These guidelines had an easy-to-understand approach, and incorporated novel flow charts to aid treatment decisions and proved popular among physicians worldwide. The guidelines consisted of three chapters (1. Definitions, 2. Ways to obtain the goal and ongoing [quality control, independent evaluation of efficacy and cost] and 3. Defined target IOP as the 'mean IOP obtained with treatment that prevents further glaucomatous damage'). It was recognised that the rate of functional decay follows different courses in patients but the point of significant functional impairment and time to start treatment needed to be defined.

In 2003, the second edition of the EGS glaucoma guidelines were published. These were divided into five chapters (1. Introduction with summaries of glaucoma randomised controlled trials [RCTs], 2. Examination, 3. Definitions, 4. Treatment modalities, and 5. Treatment strategies and flow charts). These guidelines emphasised evidence rather than consensus, took a more patient-centred approach and included concepts such as first line versus first choice, individualised target IOP and avoidance of unnecessary treatment. The third edition of the EGS Guidelines appeared in 2008 with the following modified mission statement:

"In general terms, the goal of glaucoma treatment is to maintain the patient’s visual function and related QoL, at a sustainable cost. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation. QoL is linked with visual function, and, overall, patients with early to moderate glaucoma damage have good visual function and modest reduction in QoL."

This edition of the EGS Guidelines was divided into four chapters (1. Introduction [with updated summaries of glaucoma RCTs and economic evaluation of glaucoma care], 2. Examination [more on gonioscopy and CCT], 3. Definitions [Rate of progression re-emphasised, angle closure and QoL refocused], 4. Treatment modalities and treatment strategies [adherence, compliance and persistence in glaucoma, flowcharts]). This edition also introduced the grading of strengths of recommendations (I = strong/relevant; II = weak) and strength of evidence (A = high [RCT], B = moderate, C = low [observational study], D = very low [consensus opinion]).

These guidelines also recognised, for the first time, that preservatives in medications may cause conjunctival side effects and toxicity to the ocular surface. To avoid this, the guidelines state that PF medication may be considered but they note that preservatives have been safely used for 30 years and the safety profile of the drug should be considered.

The 2008 EGS guidelines include various flow charts to inform treatment choices including the effects of higher or lower target IOP levels and a decision tree for the therapeutic trial of glaucoma medications to achieve optimal treatment with differing patient responses (see Figure 6). "Whom to treat" graphs are also included and these consider the level of visual impairment necessary to justify starting treatment and the varied profiles of disease course that can occur in different patients (see Figure 7). The guidelines also note that ocular hypertension is a clinical feature whereas glaucoma is a disease.

Overall, the EGS glaucoma guidelines have achieved their purpose in helping to make definitions, diagnosis, treatment patterns, and goals in glaucoma more consistent and evidence based.

The fourth edition of these guidelines, scheduled to release soon, will further standardise understanding and approaches to treatment and is much anticipated by many physicians involved in glaucoma management across Europe and worldwide.

The EGS glaucoma guidelines have been and will continue to be based on: evidence; consensus; common sense; and standard of care.

The continued development of the EGS guidelines will help ensure current best practice in glaucoma therapy is agreed by leading eye care experts and that it is adopted by physicians at treatment centres.

Conclusion of the Meeting

The use of PF-tafluprost in glaucoma has provided consistent efficacy of IOP control in both pivotal clinical trials and in 'real-world' use and...
has shown improved tolerability over other available medications. This was demonstrated in a trial in which switching patients to PF-tafluprost improved IOP and substantially decreased adverse event frequency. In future it is likely that more medications will become available as PF formulations as it is realised that the preservatives can cause toxicity at any stage and chronic use can lead to accumulating conjunctival damage before notable symptoms emerge. In addition, 24-hour monitoring of IOP is likely to become increasingly popular as the day/night variations in this parameter and consequent risks are more widely appreciated.

The establishment of guidelines in glaucoma treatment by the EGS has been a highly successful initiative that has fostered agreement on the basics such as definitions, diagnosis and best treatment goals and practice. These guidelines have matured into a group of valuable statements based on evidence, consensus and common standards and will likely continue to be a valuable tool for glaucoma care in many geographical areas.

Figure 6: Therapeutic Trial of Glaucoma Medications from the European Glaucoma Society Guidelines


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