Glaucoma, an optic neuropathy, is a major cause of vision loss worldwide, with many cases of falls in women accounted for by severe glaucomatous visual field loss. The most common form of this condition is primary open-angle glaucoma (POAG), which accounts for 60–70% of all glaucomas. If secondary open-angle glaucomas such as pseudoexfoliation are included, it is estimated that open-angle glaucomas account for more than 90% of glaucoma cases in Caucasians. Disease progression results in increasing damage to the optic nerve head and subsequent visual field loss. Such progression is associated with a substantial economic burden and reduced quality of life (QoL). The most important risk factor for POAG progression is elevated intraocular pressure (IOP), which can lead to the degeneration of optic nerve fibres through mechanical stress and/or reduced perfusion of the eye. The reduction of IOP has been shown to be the only strategy for preserving the visual field and limiting glaucoma progression. Results from long-term studies show that lowering IOP can either delay or stop disease progression in patients with POAG. Furthermore, IOP lowering is effective at early, intermediate and advanced disease stages as well as at high or normal baseline untreated IOPs.

Treatment of POAG aims to preserve visual function and QoL by limiting disease progression through IOP reduction. It is also recommended that the ophthalmologist ensure the treatment is at a cost that can be sustained by the individual or the society. The decision to treat and the choice of treatment should be based on an individualised approach, tailored to the patient (see Figure 1). The disease stage and life expectancy of the patient need to be considered as they are linked to visual function and QoL. Financial implications, side effects, drug–drug interactions, rate of disease progression and compliance to medication should also be considered as they all have an impact on the patient’s QoL. Currently, topical IOP-lowering medications, available as eyedrops, are the initial therapy in POAG patients, as recommended by the European Glaucoma Society (see Figure 2). These medications lower IOP by reducing aqueous production and/or increasing trabecular or uveoscleral outflow. Patients should initially be treated with monotherapy, which includes treatment with first-line medications, such as prostaglandin analogues/prostamides or β-blockers. The prostaglandin analogues are increasingly used as the first-choice of monotherapy because they have a convenient dosing schedule (once daily [QD]), potent IOP-lowering effects and lack of systemic side effects. Other classes of antiglaucoma medication that may be used for monotherapy include α-selective adrenergic agonists, carbonic anhydrase inhibitors and, to a much lesser extent, sympathomimetics and para-sympathomimetics.
Possible Reasons for Glaucoma Progression on Combination Therapy

The combination therapeutic approach utilises either fixed or unfixed combinations of antiglaucoma medications, including drugs such as the prostaglandin analogues, β-blockers, carbonic anhydrase inhibitors, etc. While combination therapy may allow greater lowering of IOP than monotherapy, some patients still do not achieve the target IOP level. Reasons cited for this include the lack of patient compliance to treatment and the presence of a ‘wash-out effect’. Patient compliance is a major concern with multiple medications, with a survey showing that only 32% of patients on two medications (n=31) were treatment-compliant versus 49% compliant patients on only one medication (n=41). The study also found the rate of treatment compliance to be largely influenced by daily dose frequency, forgetfulness, inconvenience and unaffordability. Another major concern with combination therapy, particularly the unfixed combinations, is the failure to deliver the complete dose of the medication. This wash-out effect occurs with eyedrops when there is a 5-minute interval between the dosing of two different medications, resulting in some of the first medication being washed out of the cul-de-sac and tear fluid, or even conjunctiva, by the second drop that is applied only a little while after the first drop. While a waiting time of five minutes between doses of the components is recommended, most patients wait for a shorter duration, which results in the first medication being partly or completely washed out. Studies show that in patients who wait for 30 seconds and two minutes between the dosing of medications, up to 45 and 37% of the first medication may be washed out, respectively, whereas a five-minute interval results in 100% of the first medication dose being delivered.

Strategies to Improve Treatment Outcomes with Combination Therapy

When choosing a combination therapy, an individualised treatment approach is needed, as previously described. This approach is based on the person’s needs and circumstances, and is expected to improve patient compliance and the achievement of treatment outcomes. In addition, the European Glaucoma Society has suggested several factors or points to consider when selecting adjunctive therapies. As a first step, only one medication should be added to the initial medication, minimising the possibility of reduced compliance. Furthermore, the additional medication should be from a different drug class since the different mechanisms of action provide cumulative effects that cannot be expected from two medications with the same mechanism of action. Two major factors to consider when selecting a combination therapy regimen are to ensure that compliance is optimised by minimising the number of drops and dosing frequency, and to consider the impact of the therapeutic approach on QoL. With regard to the type of combination therapy dosing regimen used, fixed combinations of antiglaucoma medications are much preferred over unfixed combinations. This preference is based on the former’s positive impact on the dosing schedule and QoL, and a higher rate of treatment compliance with the fixed combinations versus the unfixed combinations. The better compliance rates with the fixed medications are based on lower dosing frequency and treatment costs of the medications. The use of fixed combinations also eliminates the possibility of a wash-out effect, which is a major problem with unfixed combination therapies.

Fixed combinations of prostaglandins and β-blockers are frequently used in patients who progress on initial monotherapy. This is partly a result of initial monotherapy involving prostaglandin analogues; patients who progress on this medication are often switched to a combination therapy including a prostaglandin analogue and a β-blocker. Currently, three prostaglandin/β-blocker fixed combinations are approved in Europe for IOP reduction in patients with POAG or ocular hypertension (OHT) who are insufficiently responsive to topical prostaglandin analogues or β-blockers. The fixed combinations approved in Europe are as follows: latanoprost 0.005%/timolol (Xalacom®, Pfizer Inc., US) fixed combination; bimatoprost 0.03%/timolol (Santont®; Allergan Inc., US) fixed combination; and travoprost 0.004%/timolol (DuoTrav®, Alcon Inc., US) fixed combination.

Among these prostaglandin/β-blocker fixed combinations, the most clinical data, including long-term efficacy and safety results, are available for the latanoprost/timolol fixed combination (LTFC, QD).
Two randomised, double-masked, controlled studies have compared the efficacy of LTFC (QD) with its individual components (latanoprost, QD; timolol, twice daily [BID]) in patients with open-angle glaucoma (OAG) or OHT. Patients initially took part in a run-in period of timolol (BID, morning-dosed) and were then randomised to treatment with LTFC (QD, morning-dosed), latanoprost alone (QD, morning- or evening-dosed) or timolol alone (BID, morning-dosed). After six weeks of treatment, all patients were treated with LTFC alone (QD, morning-dosed) for a further six months. Results at six-month treatment follow-up showed a greater reduction in diurnal IOP with LTFC versus its individual components. In particular, LTFC therapy resulted in an additional diurnal IOP reduction of up to 1.2mmHg versus latanoprost alone (p<0.005). Furthermore, these studies showed morning-dosed LTFC to be safe, well-tolerated and effective over the 12-month treatment period. However, evening dosing can be expected to result in greater IOP-lowering activity. A recent study has evaluated whether evening dosing of LTFC is effective at lowering IOP in POAG patients. This was an observer-masked, active-controlled study in which patients with POAG (n=37) initially went medicine-free for six weeks and were then randomised to LTFC alone (QD, morning-dosed) or timolol alone (BID, morning-dosed). After six weeks of treatment, all patients were treated with LTFC alone (QD, morning-dosed) for a further six months. Results at six-month treatment follow-up showed a greater reduction in diurnal IOP with LTFC versus its individual components. In particular, LTFC therapy resulted in an additional diurnal IOP reduction of up to 1.2mmHg versus latanoprost alone (p<0.005). Furthermore, these studies showed morning-dosed LTFC to be safe, well-tolerated and effective over the 12-month treatment period. However, evening dosing can be expected to result in greater IOP-lowering activity. A recent study has evaluated whether evening dosing of LTFC is effective at lowering IOP in POAG patients. This was an observer-masked, active-controlled study in which patients with POAG (n=37) initially went medicine-free for six weeks and were then randomised to LTFC alone (QD, morning-dosed) or latanoprost alone (QD), both dosed in the evening. After eight treatment weeks, patients were crossed over to the opposite treatment for a further eight weeks. Results showed that evening dosing of LTFC can result in an additional reduction in diurnal IOP of up to 1.2mmHg versus evening-dosed latanoprost alone (p<0.005). The degree of IOP reduction achieved with evening-dosed LTFC is much greater than that observed in studies where a morning dosing protocol for LTFC was used. In light of these findings, there is a shift towards an evening dosing schedule for LTFC. Nevertheless, the label for LTFC indicates that the dose can be given at any time of day, which allows therapy to be tailored to the patient’s lifestyle and compliance.

Long-term efficacy data for LTFC are now available and show that this fixed combination can maintain its effectiveness over a long period. A recent study utilised data from the glaucoma database of the Glasgow Royal Infirmary, which is a real-life database. The data were from patients with POAG or OHT (n=59) who required additional IOP lowering because monotherapy with $\beta$-blockers produced a partial and insufficient lowering of their IOP. The interim three-year data (see

### Table 1: Interim Three-year Safety Data for the Latanoprost/Timolol Fixed Combination in Patients with Open-angle Glaucoma or Ocular Hypertension (n=974)

<table>
<thead>
<tr>
<th>Safety Parameters</th>
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<th>No IIP</th>
<th>No Iris Photo Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>16.1</td>
<td>46.5</td>
<td>37.4</td>
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<tr>
<td>≥1 AE</td>
<td>55.4</td>
<td>53.2</td>
<td>-</td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>1.3</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td>6.4</td>
<td>7.1</td>
<td>-</td>
</tr>
</tbody>
</table>

IIP = increased iris pigmentation; SAE = serious adverse event.


Figure 2: Recommended Treatment Pathway for Primary Open-angle Glaucoma Patients

Figure 2 illustrates the recommended treatment pathway for primary open-angle glaucoma patients. It shows the different steps and considerations for managing IOP, including the use of monotherapy and combination therapy. The pathway is designed to ensure effective IOP control while also considering patient-specific factors such as compliance and adverse reactions. This approach helps in tailoring pharmacological therapy for the progressing primary open-angle glaucoma patient.
Glaucoma

Table 1) showed that the LTCF is safe and well-tolerated for long-term OAG/OHT treatment. There were very few cases of increased iris pigmentation, a very low rate of LTCF-related serious adverse events and no reported deaths. The study results also showed that LTCF has long-term efficacy, with the mean IOP reduction being stable over the three years (mean IOP change over three-years -4.6±3.5mmHg).

Conclusions

Glaucoma progression leads to increasing treatment costs and reduced QoL. Reduction of IOP in glaucoma generally and specifically in POAG has proved to be the only viable strategy to limit disease progression and preserve visual function and QoL. Patients are initially treated with monotherapies but often experience disease progression, which is frequently a result of inadequate IOP lowering. A combination therapeutic approach may be used to achieve the target IOP level in patients who do not achieve optimal IOP reduction. When considering the combination therapy, several factors need to be considered, particularly the use of as few medications as possible, thereby optimising patient compliance to treatment. The fixed combination preparations are highly preferable over the unfixed combinations, particularly because the former are associated with a higher compliance rate. Among the fixed combinations, LTCF (QD) has been most extensively studied and has been shown to be more effective than either of its individual components. It has IOP-lowering effects whether dosed in the morning or the evening, allowing effective treatment tailoring, although there is now a shift towards an evening dosing schedule. Recent long-term data have shown LTCF to be effective, well-tolerated and safe over a three-year treatment period in glaucoma patients who did not achieve the target IOP with monotherapy.

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