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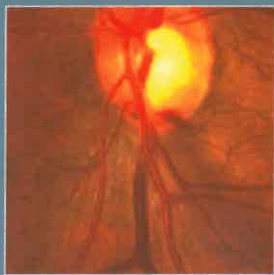
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# GLAUCOMA

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# Fixed Combination Therapies in Glaucoma

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## Summary

Fixed combination drugs can provide effective IOP control, enhance adherence and convenience, eliminate the washout effect, and significantly reduce exposure to preservatives. In real life practice, FCs can often be superior to unfixed concomitant therapy. There is still however, limited verification for the benefits accrued and little is known concerning the comparative efficacy between the newer FCs. Studies are needed to explore a number of clinically important issues between fixed and unfixed therapy, for example, adherence, convenience, drug utilization, quality of life and cost-benefit measures. Whether FCs should be employed as initial therapy in at-risk glaucoma patients and if this will improve long-term outcome requires future elucidation. Although a number of benefits can be assumed, only tentative conclusions can be drawn for their role in glaucoma therapy today. As yet, there is no information on whether FCs improve long-term clinical outcome and this will be a promising line of future research. The possibility exists that this relatively new and rapidly expanding class of medications may prove instrumental in improving management and prognosis in glaucoma.

## Introduction

The prescription of a single ocular hypotensive medication is common initial treatment for glaucoma, but over time the intraocular pressure (IOP) may rise again, requiring a second medication to be added. Current evidence suggests that approximately 50% of patients with primary open-angle glaucoma in the USA require adjunctive therapy within 2 years.<sup>1</sup> In the Collaborative Initial Glaucoma Treatment Study<sup>2</sup> more than 75% of patients in the medically treated group, required two, or more medications after the first 2 years, to attain a predetermined target IOP with a mean reduction of just 35%. Adjunctive therapy may be needed in even greater proportions for other types of glaucoma, or in an advanced stage of the disease, when a greater pressure reduction (40% or more) may be targeted to minimize progression. When the target IOP is not achieved with a single agent, combined therapy using drugs with different mechanisms of action is recommended.<sup>3</sup> However, multiple local therapies may be associated with more local and systemic side effects,<sup>4</sup> greater toxicity, a higher incidence of ocular signs and symptoms of ocular surface disease, and lower compliance.<sup>5-7</sup> Fixed combinations (FCs) of two anti-glaucoma drugs have been formulated in order to attain a greater reduction in IOP than for single agents, to allow fewer doses, to accord less exposure to preservatives<sup>4</sup> and to optimize adherence.

## FIXED COMBINATIONS AND ADHERENCE

For systemic diseases, oral fixed-dose drug combinations were introduced several years ago to improve adherence. Published evidence from several medical specialties suggests that almost half of patients with chronic, asymptomatic diseases do not take their medications as prescribed.<sup>8,9</sup> Unfortunately, inadequate adherence may diminish drug efficacy and lead to worsening health problems. Diminished adherence may inflate the cost of health care by increasing the rate of complications, medical visits and emergency hospital admissions. A meta-analysis of multiple trials has shown that fixed-dosed combinations for systemic hypertension accord greater adherence, and persistence with therapy, than combined complementary medication.<sup>9</sup>

Between 28 and 55% of glaucoma patients on long-term topical therapy have been reported not to adhere to their prescribed topical treatment regimen.<sup>5,10</sup> Indeed, reduced adherence may contribute significantly to progression of blindness in treated glaucoma patients. Frequent dosage and complex treatment regimens are significant contributory factors.<sup>9,11,12</sup> For systemic chronic disease, the availability of oral fixed-dose combinations has simplified adjunctive medication regimens,<sup>13</sup> improved adherence,<sup>9</sup> reduced costs, decreased adverse events and improved clinical outcomes.<sup>9,13-17</sup> In like manner, topical FCs for glaucoma treatment may accord similar advantages, but to date, the precise impact of FCs on adherence with topically administered medication remains to be elucidated. A recent study comparing fixed versus concomitant unfixed treatment in glaucoma<sup>17a</sup> investigated, for the first time, the impact of dosing upon the rate of adherence and ocular surface health. This prospective, 6-month, parallel, observational study enrolled 142 patients with open-angle glaucoma or ocular hypertension whose IOPs were well controlled and who received either unfixed therapy comprising latanoprost once in the evening and timolol twice daily, or fixed therapy in the form of latanoprost/timolol FC once in the evening. Adherence was monitored electronically with the Medication Event Monitoring System (MEMS) Caps device. The adherence rate was found to be significantly better in the FC group at 3 (75.6% vs. 61.2%) and 6 months (73.0% vs. 57.3%) of follow-up ( $p = 0.001$  for both comparisons). All investigated signs of ocular surface disease were significantly worse in the unfixed group at every evaluation ( $p < 0.01$  for all comparisons). This trial has for the first time provided verification of the benefits accrued in terms of adherence rate and ocular surface health with fixed compared with unfixed combination therapy.

Several studies have shown that patients taking glaucoma medications more than twice daily, tend to demonstrate the least adherence.<sup>5,10,17</sup> However, comparisons of adherence with once-daily compared with twice-daily topical medication have yet to be carried out. It is worth noting that a study by Robin and Covert<sup>18</sup> reported that glaucoma patients being treated with adjunctive unfixated glaucoma regimens show worse adherence as compared with those on once-daily monotherapy. Future studies are needed to establish the precise impact of FCs on adherence specifically in glaucoma.

### FIXED COMBINATIONS AND PRESERVATIVES

Preservatives are important components of ophthalmic preparations, suppressing microbial growth and preventing decomposition of the active drug. Benzalkonium chloride (BAK), a quaternary ammonium compound, is the most commonly used preservative in ophthalmic preparations (concentration range: 0.004–0.02%). However, BAK may have several adverse effects on the eye; first, for the pre-corneal tear film it may decrease stability, turnover and production. It may also have a detergent effect upon the lipid layer, resulting in an increased rate of evaporation. Second, in the conjunctiva, BAK may also impair the tear film, by decreasing goblet cell density.<sup>19</sup> Impression cytology studies have demonstrated inflammation, squamous metaplasia, and subconjunctival fibrosis<sup>20</sup> which are exacerbated with increased frequency and prolonged duration of administration.<sup>21</sup> Third, BAK may diminish corneal cell viability and proliferation, impairing wound healing as well as disrupting the epithelial barrier. Lastly, BAK may induce allergy, usually a type IV cytotoxic reaction and may result in contact allergy of the eyelids, which can be difficult to differentiate from other causes of periocular inflammation.<sup>21</sup> Long-term use of BAK may, in severely affected cases, result in chronic drug-induced pemphigoid characterized by a marked and self-sustaining inflammatory process leading to cicatrizing conjunctivitis and shortening of the conjunctival fornices.

Cumulative evidence indicates that the chronic, low-grade conjunctival inflammation associated with long-term anti-glaucoma therapy may constitute an important risk factor for enhanced scarring and subsequent failure of filtration surgery.<sup>21,22</sup> Therefore, glaucoma patients potentially benefit by minimizing long-term exposure to BAK or by using agents with less toxic preservatives. Accordingly, when adjunctive therapy is indicated, prescribing a FC rather than unfixated therapy will significantly reduce exposure to preservatives. Indeed, this may be partly the reason why in regulatory trials FCs manifest a lower incidence and severity of adverse events compared with unfixated therapy, with a similar prevalence to that shown by monotherapy agents.<sup>23,24–26</sup>

Although preservative-free FCs will eliminate preservatives completely, FCs without BAK may also confer a long-term benefit and reduce ocular surface toxicity since BAK is thought to be the most toxic preservative. There is still however a limited range and availability of preservative-free, or BAK-free FCs in many countries. Such choices include preservative-free dorzolamide/timolol FC (Cosopt PF, Merck Inc., Whitehouse Station, NJ, USA) and travoprost/timolol FC preserved with polyquaternium-1.

### ADVANTAGES OF FCS IN CLINICAL PRACTICE

The primary reason for the development of glaucoma FCs is that by improving patient adherence, they may also improve long-term prognosis. However, the relationship between FCs and improved visual prognosis has yet to be demonstrated in a controlled study. Certainly, FCs enhance the convenience of chronic glaucoma therapy by reducing the number of medication bottles and eye drops, as well as potentially decreasing the cost of daily therapy.<sup>4,24</sup>

With regard to efficacy, FCs generally offer more IOP lowering than each of their components alone, whereas their tolerability and safety profile is almost as good as that of their individual constituents.<sup>24</sup> In clinical practice, FCs may provide better IOP control in some patients than unfixated combined therapy,<sup>25</sup> presumably on account of elimination of the wash-out effect from the second drop as well as enhanced convenience associated with improved adherence. A pertinent study<sup>25</sup> comparing the dorzolamide/timolol FC to the concomitant administration of dorzolamide and timolol showed a significant efficacy advantage (1.7 mmHg) for the FC. The amount of information on the effects of FCs in glaucoma is increasing rapidly and the reader is referred to the comprehensive review provided by Fechtner and Realini.<sup>24</sup>

### LIMITATIONS OF FCS IN CLINICAL PRACTICE

Although FC therapy generally demonstrates significantly greater efficacy than each of its individual components, the enhanced reduction in IOP with the recently launched prostaglandin/timolol FCs has been less than was originally anticipated.<sup>26</sup> This may be due, at least in part, to the potency of prostaglandin analogs when used as monotherapy and the use of timolol only once daily in the available prostaglandin/timolol FCs. However, all the potential reasons have not been clarified. As a consequence, these FCs have yet to receive FDA approval.

Unfixated combinations generally provide a small, but non-statistical, superior IOP reduction compared to the FC containing the same medicines. Even the dorzolamide/timolol fixed combination (Cosopt™, Merck & Co., Whitehouse Station, NJ, USA), which is the best-known product of this class of drugs, when compared to its individual components (timolol dosed twice daily and dorzolamide dosed three times daily), manifested slightly lower IOP efficacy (0.7 mmHg) at the morning trough level.

It should also be recognized that FCs can diminish the flexibility of individualized patient care.<sup>26</sup> For example, all currently available FCs contain timolol 0.5% solution, which in some elderly patients may represent over-dosage. The clinician however cannot find a FC with timolol 0.25%. All currently available FCs contain timolol. It is anticipated that soon a FC without timolol (containing brinzolamide and brimonidine) will become available commercially. Another potential limitation specific to prostaglandin/timolol FCs is the timing of administration. Evening administration may lead to greater overall efficacy in the morning or daytime, but the ideal administration time for these FCs can be difficult to determine in all patients.

In a recent meta-analysis performed by Quaranta et al.<sup>27</sup> it was demonstrated that unfixated combinations of

prostaglandin analogs and  $\beta$ -blockers are to some extent more potent than their respective FCs. One possible explanation might be that patients treated with unfixed combinations will receive two doses of timolol, whereas those treated with a prostaglandin/timolol FC receive only one. Another logical explanation may be that, in four of the five analyzed studies, the FC was administered in the morning.<sup>28-31</sup> Studies with daytime measurements will overestimate the efficacy of evening-dosed prostaglandin analogs and underestimate the efficacy of morning-dosed prostaglandin/timolol FCs due to the fact that with prostaglandins the peak efficacy is seen 8–12 hours after administration. Thus, if a prostaglandin/timolol FC is dosed in the morning, its peak efficacy remains largely unrecorded, unless the IOP is measured at night. There is no perfect uniformity among registration trials and therefore it is sometimes difficult to compare the efficacy between FCs in the same therapeutic category. For example, in the travoprost/timolol FC regulatory trials, the unfixed arm included timolol dosed once a day, whereas the unfixed therapy arm of the other two prostaglandin/timolol FCs included timolol dosed twice daily. Further, the design of published studies typically includes patients with ocular hypertension, or primary open-angle glaucoma. It is not precisely known how well the new FCs control the IOP in other glaucomas (e.g. closed-angle glaucoma).

Generally, the reported adverse events of FCs are similar to those reported for their individual constituents. It is fortunate that FCs have not been associated with the emergence of unique adverse events.<sup>24,25</sup> What is noteworthy however is that, as highlighted in a systematic review, all three prostaglandin/timolol FCs are better tolerated than their respective prostaglandin monotherapies, but less well tolerated than timolol.<sup>27</sup> A good example is the study by Brandt and coworkers,<sup>32</sup> who compared the bimatoprost/timolol FC with each of its constituents and reported a significantly lower incidence of conjunctival hyperemia with the FC.<sup>32</sup> The mechanism underlying the reduction of hyperemia when a prostaglandin is used in a FC together with timolol, is not entirely clear. It has been postulated that it may be due to the  $\alpha_1$ -adrenergic agonist effect of endogenous catecholamines, which is unopposed by  $\beta_2$ -adrenergic agonists after timolol-induced  $\beta$ -blockade.<sup>33</sup> The incidence of conjunctival hyperemia has also been reduced with the other two FCs compared with that seen with the respective prostaglandin.

Since glaucoma is a 24-hour, lifetime disease, more controlled studies are needed to document the long-term 24-hour efficacy and long-term tolerability of FCs versus unfixed concomitant therapies.

## CURRENT AND FUTURE FC CHOICES IN GLAUCOMA

Currently, widely available FCs include the dorzolamide/timolol (Cosopt, Merck) and the brinzolamide/timolol (Azarga, Alcon) FCs, which are available in most countries worldwide, and the latanoprost/timolol (Xalacom, Pfizer), travoprost/timolol (DuoTrav, Alcon), bimatoprost/timolol (Ganfort, Allergan) and brimonidine/timolol (Combigan, Allergan) FCs, which are available in several countries. These drugs are generally selected as second- or third-line therapy. Which FC is superior in terms of efficacy and

tolerability is often not well documented, but the amount of evidence available is increasing rapidly, and several studies are currently underway to compare the efficacy of the newer FCs in various types of glaucoma.

There are a number of pharmacological obstacles (differences in dosing and pharmacokinetics, potential drug interactions, instability of combined molecules, etc.) that do not currently allow the introduction of other conceptually attractive FCs, e.g. combining prostaglandins and topical carbonic anhydrase inhibitors. Such new FCs may however become available in the future. Recently, the results of a phase 3 study for a new brinzolamide 1%/brimonidine 0.2% FC became available.<sup>34</sup> In this multicenter, double-masked, parallel study, the diurnal efficacy of the brinzolamide/brimonidine FC was compared to that of its individual components, when all medications were administered thrice daily in patients with open-angle glaucoma or ocular hypertension. According to this study, this FC can provide clinically meaningful incremental IOP control. Specifically, both for the 3-month primary endpoint and the 2- and 6-week secondary endpoints, the new FC achieved significantly better IOP control compared to each individual constituent. At the 3-month time point, the IOP reductions for the FC group were 5.4 to 8.4 mmHg across the time points studied, versus 4.2 to 5.7 mmHg for the brinzolamide group and 3.1 to 6.5 for the brimonidine group.<sup>34</sup> A new preservative-free FC incorporating tafluprost and timolol maleate, will become available within the next year in Europe (Santen Pharmaceutical Co., Ltd).

It is not yet known if FC therapy is appropriate for initial glaucoma therapy. Oral FCs have been found to be cost efficient and to improve clinical outcomes in several systemic chronic diseases when prescribed as initial therapy.<sup>35</sup> A FC may have an advantage as initial therapy to more rapidly reduce IOP when the patient presents with an unusually high IOP (e.g. in exfoliative or neovascular glaucoma), or with advanced damage. How early should FCs be introduced in clinical practice is currently difficult to answer. In cases with high baseline IOP, advanced glaucomatous damage, suboptimal follow-up, and limited availability of resources, consideration should be given to initial therapy with a FC even if this reduces the possibility of identification of non-responders. On the other hand, concern remains that a FC might be prescribed in real-life practice, as initial therapy, without a clear understanding of its efficacy and safety profile.<sup>24</sup> In addition, the therapeutic effect of the individual components cannot be confirmed and any adverse event may not be attributed to the correct component.

In summary, FCs filled an unmet need and offered additional choices in the medical treatment of glaucoma. By combining standardized doses of two medications in a single bottle FCs improve adherence, real-life efficacy and long-term tolerability through a variety of mechanisms. The value and future promise of FCs in glaucoma remain to be determined. To date, regulatory approvals worldwide and the salient published literature, are based on efficacy and safety comparisons between the FCs and the individual components, or the concomitant use of both constituents.<sup>35</sup> This approach however, is not ideal since it does not take into account other key benefits such as enhanced adherence, improved convenience and reduced cost to patients.

In the current management of glaucoma, inadequate adherence remains the biggest obstacle in delivering successful therapy by greatly diminishing drug efficacy in real life, which leads to under-treatment and disease progression. Further, the challenge in optimizing combined therapy in glaucoma management is to try to keep medical therapy practicable. This concept probably involves treatment with up to three drugs in two bottles, one of which would be a FC.<sup>26</sup> The possibility exists that this relatively new and rapidly expanding class of medications may prove instrumental in improving the prognosis of glaucoma.

## Drug Formulations

The search to develop effective FCs of glaucoma drugs has intensified over the last few years. A number of new combination therapies have been approved by various regulatory authorities in different countries and numerous studies have been published on the subject.<sup>36-66</sup> This section will not discuss FCs of historical interest (e.g. timolol/pilocarpine FC). It aims to briefly review the key characteristics and efficacy of those that are currently available.

### DORZOLAMIDE/TIMOLOL MALEATE FC

Fixed combination therapy in glaucoma has gained popularity in recent years principally due to the success of the dorzolamide/timolol FC (Cosopt<sup>®</sup> Merck and Co Inc, Whitehouse Station, NJ, USA). This FC was released commercially in the US and in Europe in 1998. At present this and the brimonidine/timolol FC (Combigan, Allergan), are the only FCs approved by the FDA. The pharmacology of this product is related to its two active ingredients and it is prescribed for twice-daily dosing. Regulatory data showed that this FC can lower IOP by 9 mmHg (32.7%) at peak compared with 5.4 mmHg (19.8%) and 6.3 mmHg (22.6%) for dorzolamide and timolol monotherapies, respectively.<sup>26</sup> At trough, the IOP reduction was 7.7 mmHg (27%) for the FC. The dorzolamide/timolol FC decreased IOP by a further 1.1–1.3 mmHg from timolol maleate at trough and by 2.8 mmHg at peak (2 hours after dosing).<sup>36</sup> Further, this FC showed almost clinical equivalence to unfixed concomitant therapy with the largest, but with a non-significant, difference reported at 16:00 hours (0.7 mmHg difference versus unfixed therapy). In contrast, in real-life practice, the dorzolamide/timolol FC has been shown to attain better IOP control compared with unfixed concomitant therapy,<sup>25,26</sup> owing to enhanced convenience, elimination of the wash-out effect from the second drop and improved adherence. The safety and efficacy profile of this FC have been reviewed comprehensively by Frampton and Perry.<sup>36</sup> Common ocular side effects with this FC have been mostly related to the dorzolamide component and include bitter taste and stinging/burning on instillation.

Fechtner and associates<sup>37</sup> evaluated daytime IOP of latanoprost dosed in the evening versus the dorzolamide/timolol FC and showed that the diurnal pressure control was similar with both agents. In contrast, in a complete 24-hour study Konstas and coworkers<sup>38</sup> found that this FC provided significantly better 24-hour IOP control (–0.6 mmHg) than latanoprost mainly due to the greater

efficacy of the FC at night (22:00 timepoint). In another 24-hour study, Orzalesi and associates<sup>39</sup> noted almost similar IOP control between these two products except at 09:00 when the FC was more effective. In a 24-hour study on previously untreated primary open-angle glaucoma patients, Quaranta and coworkers<sup>67</sup> observed a significant difference in 24-hour efficacy in favor of the dorzolamide/timolol FC (–1.3 mmHg;  $p < 0.0001$ ) when compared to latanoprost monotherapy. The 24-hour difference observed between the two studies<sup>38,67</sup> may be attributable to the fact that the dorzolamide/timolol FC was employed as initial therapy in the Quaranta study and thus patients may have shown a greater response to timolol.

In a larger, longer-term, randomized, prospective crossover 24-hour IOP study on 53 patients with primary open-angle glaucoma or ocular hypertension, Konstas and associates<sup>40</sup> compared the 24-hour IOP efficacy of the dorzolamide/timolol FC versus latanoprost over 2 and 6 months. After two months of therapy, the FC provided significantly better control at three time-points (10:00, 18:00 and 22:00) and for the mean 24-hour IOP ( $18.0 \pm 1.8$  vs.  $18.6 \pm 1.9$  mmHg;  $p = 0.0002$ ). However, following 6 months of chronic treatment, the mean 24-hour IOP was similar between the two medications ( $18.1 \pm 1.9$  vs.  $18.3 \pm 1.9$  mmHg). The FC still provided significantly better IOP at 2 time-points (10:00 and 22:00;  $p < 0.01$ ).<sup>40</sup> Compared to 2 months of therapy, at 6 months the FC showed similar mean 24-hour IOP, with no evidence of tachyphylaxis, whereas latanoprost manifested a further reduction of IOP (–0.3 mmHg).

The two commercially available carbonic anhydrase/timolol FCs (brinzolamide/timolol suspension and the dorzolamide/timolol solution) were evaluated in a multicenter, double-masked, parallel arm, non-inferiority study of patients with open-angle glaucoma and ocular hypertension.<sup>68</sup> The authors reported that both FCs achieved similar IOP reduction (28.4–34.9% for the brinzolamide/timolol versus 29.2–33.9% for the dorzolamide/timolol FC), thus establishing that the brinzolamide/timolol FC suspension was equally effective.

One study<sup>69</sup> has demonstrated that dorzolamide/timolol FC significantly increases superior retinal arterio-venous passage time thus increasing blood flow rate and retinal perfusion. They found that timolol had no adverse effects on the retinal circulation, but the dorzolamide component of the FC improved hemodynamics by a direct, or indirect, mechanism of action. In a comparative study between the dorzolamide/timolol and the latanoprost/timolol FCs in newly diagnosed open-angle glaucoma patients, Martinez and Sanchez<sup>70</sup> documented similar efficacy between the two medications, but reported that only the dorzolamide/timolol FC had an effect on the retrobulbar vessels in their glaucoma patients.

The dorzolamide/timolol FC has been evaluated as initial therapy in glaucoma patients with high baseline pressures. It has been documented to be a viable option in these patients demonstrating a significant IOP-lowering effect.<sup>71,72</sup> In a prospective study Henderer and associates<sup>71</sup> employed dorzolamide/timolol FC as initial therapy in 18 patients with a mean pretreatment IOP of 37.5 mmHg. Two hours after the initial dose of the FC the IOP fell to 18.2 mmHg, whereas after two months of therapy the

treated IOP varied between 21.1 mmHg at trough and 17.6 mmHg at peak (mean reduction of 40–49%).

More recently, in an experimental study on human trabecular meshwork this FC was reported to exhibit antioxidant effects.<sup>73</sup> The antioxidant effects of dorzolamide and timolol were observed on trabecular meshwork biopsy specimens and human trabecular meshwork cells exposed to hydrogen peroxide. The antioxidant effects of dorzolamide were exerted toward high and low hydrogen peroxide concentrations, whereas timolol was protective only with low hydrogen peroxide concentrations. Timolol had direct antioxidant effects related to its own metabolism. Conversely, dorzolamide exerted protective activity mainly in the presence of intact mitochondria. These findings may suggest that dorzolamide could be used in the treatment of glaucoma when trabecular meshwork damage is not advanced and the trabecular cells are viable with intact mitochondrial function.

### LATANOPROST/TIMOLOL MALEATE FC

The latanoprost/timolol maleate FC (Xalacom™, Pfizer, Inc., New York, NY, USA) was commercially released in Europe in 2001. The regulatory trials by Pfeiffer and associates<sup>41</sup> and Higginbotham and coworkers<sup>42</sup> reported the morning dosing of this FC to further reduce the IOP compared to both latanoprost dosed once daily (1.1 to 1.2 mmHg), or timolol dosed twice daily (1.9 to 2.9 mmHg, respectively). Unfortunately, the extent of IOP reduction with the morning dosing of the latanoprost/timolol FC compared to latanoprost alone was less than anticipated during development. The reason for the relative lack of efficacy has not been explained. Preclinical data suggest that the combination of the two drugs in one formulation did not adversely affect the absorption of either drug.<sup>42</sup> The bioavailability of latanoprost and timolol in the aqueous with this FC was at least as good as for the two drugs administered separately. One reason why there is less efficacy than anticipated may be because the FC was administered in the morning in both regulatory trials, whereas latanoprost alone was dosed in the evening in the Higginbotham study.<sup>42</sup> Previously, Alm and associates<sup>43</sup> as well as Konstas and coworkers<sup>44–46</sup> have consistently shown that the evening dosing of latanoprost provides lower daytime pressures than the morning dosing.

Therefore, the study design of the regulatory trials may have reduced both the daytime efficacy of the latanoprost/timolol FC, and the difference between the FC and its individual components. In contrast, a 24-hour study by Konstas and associates<sup>46</sup> showed that when both the latanoprost/timolol FC and latanoprost are dosed in the evening a wider efficacy separation exists between the two drugs (2.5 mmHg) over 24 hours. Further, in a more recent crossover study,<sup>66</sup> the 24-hour IOP fluctuation was significantly narrower when the latanoprost/timolol FC was administered in the evening (3.2 mmHg) compared with timolol monotherapy (4.4 mmHg). This level of 24-hour fluctuation with the evening-dosed FC was less than the level of fluctuation reported in previous diurnal studies<sup>44,53</sup> with morning dosing (3.9–4.3 mmHg). The reason for the reduced 24-hour fluctuation with the evening administration may be due to the greater efficacy of the latanoprost constituent of the FC in reducing daytime pressures.

This effect was also shown in the trials comparing this FC to the concomitant administration of the individual components by Diestelhorst and Larsson.<sup>47,48</sup> The first trial compared the morning dosing of latanoprost/timolol FC versus unfixed therapy (timolol dosed twice and latanoprost dosed in the evening) and detected a significant 1.1 mmHg difference in favor of the unfixed therapy.<sup>47</sup> In contrast, in a more recent trial the same group<sup>48</sup> compared the evening dosing of the FC versus the same unfixed therapy regiment and documented clinical equivalence between the two therapies (0.3 mmHg). To date, the only direct comparison between morning and evening dosing of the latanoprost/timolol FC has been performed by Takmaz and coworkers.<sup>74</sup> This group compared the 24-hour efficacy of morning versus evening dosing of LTFC and reported significantly better efficacy with the evening dosing. The evening administration of latanoprost/timolol provided a greater mean 24-hour IOP reduction, lower 24-hour fluctuation of IOP as well as two timepoints (06:00 and 10:00) with lower IOP.

Stewart and coworkers<sup>49</sup> noted that latanoprost/timolol FC dosed in the evening was more effective at 8–12 hours after dosing, and for the end of the daytime diurnal curve, than brimonidine and timolol dosed concomitantly. In addition, Garcia-Sanchez and associates<sup>50</sup> showed in a 6-month, multicentered, parallel study that latanoprost/timolol FC reduced the pressure more than the concomitant administration of timolol and brimonidine over a three-point diurnal curve ( $16.9 \pm 2.8$  versus  $18.2 \pm 3.1$  mmHg). Finally, Stewart and coworkers<sup>51</sup> found that the latanoprost/timolol FC provided equal efficacy to latanoprost and brimonidine (dosed twice daily) in a three-point diurnal pressure curve.

Compared to the dorzolamide/timolol FC given twice daily, Shin and associates<sup>52</sup> observed that latanoprost/timolol FC reduced IOP by approximately 1.0 mmHg further, over three daytime points. In contrast, Konstas and coworkers<sup>53</sup> reported similar efficacy between latanoprost/timolol and dorzolamide/timolol FCs over a 12-hour diurnal curve with the IOP measured every 2 hours. Topouzis and associates<sup>54</sup> evaluated the latanoprost/timolol versus the travoprost/timolol FCs, both dosed once daily in the morning, in a parallel, multicenter study. The two FCs were found to be equivalent except for one timepoint (09:00) when the travoprost/timolol FC was statistically more effective when all visits were considered across the 6-month study period.

### TRAVOPROST/TIMOLOL MALEATE FC

The travoprost 0.004%/timolol maleate 0.5% FC (DuoTrav™, Alcon, Inc., Fort Worth, Texas, USA) has gained regulatory approval in Europe and many other countries worldwide except the US. This FC is indicated for the treatment of patients with open-angle glaucoma or ocular hypertension needing further IOP reduction from a beta-blocker or prostaglandin analog. Two randomized controlled trials have compared the travoprost/timolol FC with the efficacy of its constituents. Barnebey and associates<sup>55</sup> showed that patients treated with the travoprost/timolol FC dosed in the morning exhibit a further reduction of IOP from baseline of 1.9 to 3.3 mmHg more than timolol monotherapy and 0.9 to 2.4 mmHg more than travoprost alone.

In another study, Schuman and coworkers<sup>56</sup> demonstrated that the mean IOP ranged from 16.2 to 17.4 mmHg with the travoprost/timolol FC dosed in the morning compared with 15.4 to 16.8 mmHg with the concomitant administration of travoprost and timolol. In a third study with a similar design, Hughes and associates<sup>57</sup> noted the mean IOP ranged between 15.2 and 16.5 mmHg in the patients using the travoprost/timolol FC compared with 14.7 to 16.1 mmHg in the concomitant therapy group. Consequently, morning dosed travoprost/timolol FC is expected to provide additional lowering of IOP to patients insufficiently controlled on prior beta-blocker or prostaglandin analog monotherapy and similar IOP control to concomitant therapy with these medications.

Despite the labeling in Europe for morning or evening dosing, little information is available evaluating the evening dosing of the travoprost/timolol maleate FC. Previous research has suggested that prostaglandin analogs dosed in the evening may provide lower daytime mean IOP and reduced 24-hour IOP fluctuation. In the first study to directly compare the 24-hour efficacy between morning and evening administration of the travoprost/timolol FC, Konstas and coworkers<sup>58</sup> demonstrated that both morning and evening dosing of this FC provided a statistically significant reduction from untreated baseline at each time point and the 24-hour pressure curve. However, when both treatment regimens were compared directly, the evening dosing demonstrated a lower absolute IOP, and greater, statistically significant reduction from untreated baseline, for the 24-hour IOP curve and individual daytime time points at 10:00, 14:00, 18:00 and 06:00 hours.<sup>58</sup> In contrast, morning dosing provided a slightly lower, non-significant, reduction in pressure at 22:00 and 02:00 hours. This study adds more information for the preferred dosing for all three prostaglandin/timolol fixed combinations. It suggests that although both dosing regimens provide effective 24-hour IOP reduction, the evening dosing demonstrates better quality of 24-hour IOP control.

These results are consistent with past studies by Alm et al.<sup>43</sup> and Konstas et al.<sup>44-46</sup> that have indicated that prostaglandin analogs (latanoprost, travoprost, or latanoprost added to timolol) when dosed in the evening consistently provide lower daytime pressures when compared to morning dosing. This may be due to the fact that prostaglandins demonstrate their peak efficacy 8–12 hours after dosing. Consequently, it can be expected that an evening dosed prostaglandin/timolol FC will generally provide its maximum pharmacologic effect, and its best ocular hypertensive control, in the daytime. This fact is clinically important because most 24-hour IOP evidence indicates that the IOP is usually higher in the morning and during the daytime.

There is limited information available concerning the comparative efficacy of the newer FCs in exfoliative glaucoma. In a direct comparison between travoprost/timolol and latanoprost/timolol FCs over 24 hours Konstas and coworkers<sup>75</sup> reported that the travoprost/timolol FC provided statistically greater 24-hour efficacy as well as lower fluctuation and peak 24-hour IOP than the latanoprost/timolol FC in patients with exfoliative glaucoma.

A new formulation of travoprost/timolol FC preserved with polyquaternium-1 rather than BAK is currently

replacing the BAK-containing formulation in most countries.<sup>76</sup> Given that BAK is supposed to enhance the penetration of co-administered molecules, concern arises that removing BAK from a formulation may reduce to a certain extent ocular penetration of the active drug ingredient and thus reduce overall clinical efficacy. To address this concern, Kitazawa and coworkers<sup>77</sup> conducted a prospective, randomized, double-blind comparison of the safety and efficacy of travoprost/timolol FC preserved with BAK versus the same FC without BAK. In this non-inferiority trial, 388 subjects with ocular hypertension or POAG were treated with one of the two formulations for 6 weeks. The mean IOP reduction, pooled across all visits and time-points, was 8.0 mmHg in the travoprost/timolol BAK-free group and 8.4 mmHg in the travoprost/timolol with BAK group ( $p = 0.09$ ). The mean pooled difference between groups was 0.4 mmHg (95% CI  $-0.1$  to  $0.8$ ), demonstrating non-inferiority for the BAK-free formulation compared with the BAK-preserved formulation. The most common drug-related ocular adverse event was ocular and conjunctival hyperemia, occurring in 11.8% of the BAK-free group and 13.0% of the BAK-containing group. The findings by Kitazawa et al.<sup>77</sup> suggest that removing BAK from the formulation had no measurable effect on its IOP-lowering efficacy. The current literature has not yet offered sufficient controlled evidence evaluating the efficacy and safety of the travoprost/timolol BAK free FC versus other available FCs, such as the dorzolamide/timolol, the latanoprost/timolol, the bimatoprost/timolol and the brimonidine/timolol FCs. Future comparative studies may help the clinician to select the most efficacious FC therapy for their patients. Furthermore, no controlled study has documented as yet the long-term pressure control of the travoprost/timolol BAK-free FC therapy. Future comparative studies may verify the benefits upon adherence, long-term tolerability and ocular surface health as well as the ultimate surgical success of those patients who are now treated with medications that do not contain BAK.

## BIMATOPROST/TIMOLOL MALEATE FC

The bimatoprost/timolol FC eye drops solution (Ganfort™, Allergan, Inc., Irvine, CA, USA) is composed of bimatoprost 0.03%, and timolol 0.5%. This FC is employed as a once-daily topical ocular therapy for the reduction of elevated IOP in patients with open-angle glaucoma, or ocular hypertension for whom monotherapies provide insufficient IOP control. The individual active components of this FC are established therapeutic agents with well-documented IOP efficacy. Bimatoprost and timolol have complementary mechanisms of hypotensive action. Bimatoprost is believed to lower IOP mainly by increasing uveoscleral outflow whereas timolol lowers IOP by reducing aqueous humor formation.

The overall development program for the bimatoprost/timolol FC involved 1964 patients. In all four studies conducted and submitted to EMEA for approval, the administration of the FC was in the morning. These data<sup>32</sup> consisted of two 12-month, three-armed, parallel design trials in which the morning administration of this FC was compared to once-daily evening dosing of bimatoprost and twice-daily dosing of timolol. In these studies, the reduction provided

by the bimatoprost/timolol FC with morning dosing was less than might be anticipated versus bimatoprost monotherapy. The reasons for the relative lack of efficacy have not been fully explained as yet. However, as previously discussed, it may be because the FC was instilled in the morning in these regulatory trials, whereas bimatoprost monotherapy was dosed in the evening. Bimatoprost, like all prostaglandin analogs, is generally dosed at night and previous data have demonstrated that the evening dosing provides lower daytime IOP.

Hommer and coworkers<sup>59</sup> reported the results of a double-masked, parallel, 3-week study where the bimatoprost/timolol FC was not inferior to the unfixed therapy of bimatoprost and timolol dosed twice daily at all three time points measured. The mean diurnal IOP control obtained with the FC after 3 weeks of therapy (16.1 mmHg) was similar in terms of hypotensive efficacy with the unfixed therapy (15.6 mmHg) and 1 mmHg better than bimatoprost monotherapy (17.1 mmHg). In this study, the FC therapy group manifested a lower propensity for conjunctival hyperemia (19.3% vs. 25.6% for the unfixed therapy group and 27.8% for bimatoprost) although the among-group difference was not statistically significant. Interestingly, from the overall regulatory data, it is evident that the proportion of patients who reported at least one adverse reaction with bimatoprost/timolol FC was significantly lower than with bimatoprost monotherapy, i.e. 48% vs. 60%, ( $p = 0.001$ ). Likewise, the rate of discontinuation because of adverse events was 3.6% in the FC group as opposed to 7.9% in the bimatoprost monotherapy group ( $p = 0.008$ ). These differences may be clinically relevant, and may lead to better adherence and persistence to those patients treated chronically with the FC. The reasons for the decreased incidence of adverse events seen in the FC group remain unclear. It may be due to the direct effect of timolol that may limit the incidence of hyperemia by reducing the vasodilatory effects of endogenous catecholamines at the relevant conjunctival  $\beta$  receptors. Further, there may also be a benefit from the reduction in the amounts of the active drug and the preservative delivered to the ocular surface.

A recent 4-week study<sup>60</sup> has suggested the possibility that the evening administration of bimatoprost/timolol FC may be more effective than the evening dosing of the latanoprost/timolol FC, but this requires confirmation from a larger, adequately powered study. In a recent study employing a crossover design, the 24-hour IOP characteristics of evening and morning bimatoprost/timolol FC were compared in a group of patients with exfoliation.<sup>78</sup> Despite the statistical superiority of evening dosing (10.2 mmHg, 35.3% reduction) compared with the morning dosing (9.8 mmHg, 33.8% reduction), this 0.4 mmHg 24-hour difference may not be clinically meaningful. In the future it is clinically important to compare the evening versus the morning dosing of the bimatoprost/timolol FC in other glaucomas to establish which dosing is more effective and to compare this FC with the other available FCs with evening dosing.

In a recent meta-analysis Aptel and coworkers<sup>79</sup> demonstrated that all three prostaglandin/timolol FCs provide greater IOP reduction and a lower rate of hyperemia than the three respective prostaglandin monotherapies. This meta-analysis confirmed that prostaglandin/timolol FCs

can significantly enhance the efficacy of prostaglandin monotherapies and, at the same time, reduce one of their important side effects, conjunctival hyperemia. Further, this meta-analysis reported bimatoprost/timolol to be somewhat more effective than the other two prostaglandin/timolol FCs. This conclusion should be interpreted with some caution since the direct comparisons between bimatoprost/timolol and latanoprost/timolol FCs show a high level of heterogeneity.<sup>80</sup> Moreover, the direct comparison between bimatoprost/timolol and travoprost/timolol FCs is based on a single study by Centofanti and coworkers.<sup>81</sup> In this study patients who responded inadequately to the latanoprost/timolol FC were switched to either bimatoprost/timolol, or travoprost/timolol FC therapy. This study introduces clinical heterogeneity since the study patients were, to a certain extent, suboptimal responders to either timolol, latanoprost or the latanoprost/timolol FC.

In a recent 24-hour study Konstas and coworkers<sup>82</sup> investigated the efficacy of bimatoprost/timolol FC compared with latanoprost as initial therapy in selected exfoliation patients with high baseline pressure. This study suggested that bimatoprost/timolol FC was more effective than latanoprost in reducing 24-hour IOP in exfoliation patients with high baseline IOP at least over the short term. The mean 24-hour IOP difference between the two agents was clinically meaningful (2.3 mmHg) in these high-risk patients. Other noteworthy differences with bimatoprost/timolol FC were the significantly lower mean peak and trough 24-hour IOP. Finally, the FC provided significantly better IOP control at every individual time point evaluated in this study with a similar rate of adverse events. Future research on the long-term 24-hour efficacy of bimatoprost/timolol FC employed as initial therapy and the progression rate with this more aggressive treatment algorithm is needed.

## BRIMONIDINE/TIMOLOL MALEATE FC

The brimonidine/timolol fixed combination (Combigan™, Allergan, Inc., Irvine, CA, USA) has been approved in many countries worldwide. Craven and coworkers,<sup>61</sup> demonstrated that the brimonidine/timolol FC, compared to each of its individual components reduced the morning trough pressure by 28% from no treatment and 1.6 mmHg from timolol alone. However, the afternoon time point at 15:00 showed only a 0.6 mmHg further reduction in pressure while at 17:00 no additional decrease was observed, compared to timolol alone. Further, Sherwood and associates<sup>62</sup> recently showed, in a meta-analysis of the two regulatory trials, that brimonidine/timolol FC reduced the pressure more than the individual components at all time points except compared to brimonidine at 17:00 (dosed three times daily). The range of reduction was 4.4 to 7.6 mmHg with brimonidine/timolol fixed combination, 2.7 to 5.5 mmHg with brimonidine and 3.9 to 6.2 mmHg with timolol.

In another comparison, Goni and coworkers<sup>63</sup> showed that the brimonidine/timolol FC provided almost equal efficacy (0.4 mmHg difference) to the unfixed combination of its individual components (brimonidine and timolol dosed twice daily) with reductions ranging from 4.4 to 5.3 mmHg in both groups at morning trough and peak time points. In addition, Konstas and associates<sup>64</sup> showed that the brimonidine/timolol FC offered equal 24-hour pressure



control to the unfixed components, both dosed twice daily, in a crossover trial. The range of pressure reduction from untreated baseline was 19–26% for both treatment groups.

Compared to other FC therapies, Arcieri and associates,<sup>65</sup> in a crossover study on 30 patients found equivalent pressures between the brimonidine/timolol ( $15.0 \pm 2.1$  mmHg) and the dorzolamide/timolol FCs ( $15.4 \pm 2.1$  mmHg) using a three-point diurnal curve. In contrast a recent 24-hour multicenter study comparing the dorzolamide/timolol and the brimonidine/timolol FCs<sup>83</sup> showed that the dorzolamide/timolol FC demonstrated a lower mean 24-hour IOP compared to the brimonidine/timolol FC (mean difference:  $-0.7$  mmHg, 95% confidence interval:  $(-1.0, -0.3)$ ,  $p < 0.0001$ ).

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