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EDITORIAL *free on line*

Prostaglandin-timolol fixed combinations efficacy: myth or reality?

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INTRODUCTION

Prostaglandin-timolol fixed combinations (PTFCs) were introduced several years ago to improve adherence to chronic topical medical therapy in glaucoma (1). Published work has stressed that between 28% and 55% of patients do not adhere to their prescribed treatment regimen (2). Insufficient adherence may diminish efficacy, lead to glaucoma progression, and contribute to the current incidence of blindness among glaucoma patients. A recent meta-analysis of medical therapeutic trials has shown that non-adherence to medical therapy is reduced by 24%-26% with fixed-dose combination regimens, compared with unfixed concomitant therapies (3). Theoretically, topical fixed combinations should provide similar advantages in glaucoma treatment as in other fields of medicine. Nevertheless, as yet the precise impact on adherence of all glaucoma fixed combinations remains to be determined. Although the available information relevant to fixed combinations is increasing rapidly, comprehensive evidence is needed to demonstrate to what extent this class of medications improves adherence, decreases adverse events, and improves long-term clinical outcome.

The availability of the PTFCs has simplified adjunctive medication regimens. These combinations generally offer more intraocular pressure (IOP) lowering than each of their components alone, whereas their safety profile is almost as good as their individual constituents (1). Importantly, in real life practice these combinations may provide better IOP control in some patients than unfixed concomitant therapy. Presumably this is due to the combined effects of enhanced convenience, elimination of the washout effect from the second drop, and improved adherence. Nevertheless, although PTFCs generally demonstrate greater efficacy than each of their individual components, the enhanced reduction in IOP with these medications has been less than was originally anticipated. This may be due, at least in part, to the potency of prostaglandin analogues, when used as monotherapy, and the use of timolol only once daily in PTFCs. It should also be borne in mind that to date there is limited published information evaluating the complete efficacy of PTFCs beyond 2-3 timepoints during the daytime. Interestingly, comparisons over 24 hours have generally demonstrated greater efficacy for these fixed combinations compared with their prostaglandin constituents (4-6). Other factors (time of administration, methodology of studies, baseline IOP) may also play a part in these comparisons. To remove this ambiguity, in the future it will be important to assess the therapeutic equivalence of PTFCs versus unfixed therapy throughout the 24-hour period. Studies are also needed to evaluate the efficacy of this therapeutic category over the long term.

In the current ophthalmic literature it is generally difficult to assess and critically compare the efficacy reported for each fixed combination. There is no perfect uniformity among registration trials and it is even more difficult to compare results from diverse phase IV trials. This is a common problem in medicine since the enormous growth of biomedical publications has yielded a massive literature that is beyond the ability of the average clinician to handle. Practicing physicians seeking answers to specific queries commonly find an excess of material of varying quality and conflicting findings that make clinical decision-making complex. The interpretation is limited by the presence of numerous small studies, which often do not reach either statistical significance or clinically meaningful outcomes.

Meta-analysis, a statistical method of combining the results of multiple studies, can harmonize this discordant literature. It provides the potential to address questions that individual studies lack the power to address. Most importantly, it offers a framework to investigate and explain between-study heterogeneity, potentially affording insights into the mechanisms of effects and a means to identify populations most likely to benefit from a specific

therapy or intervention. The first meta-analysis has generally been credited to the statistician Karl Pearson in 1904 (7) although Glass first defined the term meta-analysis in 1976 in the social science literature (8). Since then the merits and perils of meta-analysis continue to be debated in the medical literature (9-12). It is to be emphasized, however, that evidence is evolving; new studies are continually being published and their results may accord or be at variance with older studies. In some cases, this can result in revisions to the conclusions of previously published meta-analyses (13-16). Moreover, the possibility exists that some meta-analyses that ignore the wider spectrum of clinical trials, such as unpublished studies, could lead to narrow, misleading interpretations (15).

The meta-analysis by Aptel et al, published in this issue, shows that all 3 PTFCs provide greater IOP reduction and a lower incidence of hyperemia than the 3 respective prostaglandin monotherapies. The direct comparisons reported herein suggest greater efficacy for the bimatoprost-timolol fixed combination compared with the latanoprost-timolol and the travoprost-timolol fixed combinations. This meta-analysis confirmed that PTFCs can significantly enhance the efficacy of prostaglandin monotherapies and, at the same time, reduce one of their important side effects, conjunctival hyperemia. The present study confirms what we often see in clinical practice. As stated previously, the incremental efficacy of PTFCs, although statistically significant and clinically meaningful, can be modest. This may reflect the robust efficacy and tolerability profile of prostaglandin monotherapies. It is now more difficult to reach further IOP reduction without compromising adherence. It remains to be seen what constitutes a meaningful incremental IOP reduction. For at-risk and progressing patients even a 1 mmHg further IOP reduction is important. Therefore, the findings of this meta-analysis are most welcome: adding timolol to a prostaglandin analogue in a fixed combination provides measurable clinical value in terms of efficacy and tolerability.

It is difficult to compare the results of the present meta-analysis to those of others. Three previously published meta-analyses (17-19) reported that, in agreement with this work, the efficacy of PTFCs is significantly greater than that of each of their separate components. This refers to the situation where the trial drug (timolol, prostaglandin, or PTFC) is initiated in treatment of naive patients, or in established patients after an appropriate washout period. However, it is to be emphasized that a conventional meta-analysis is not the appropriate technique to apply a ranking of drugs, in this case IOP-lowering drugs, if appropriate head-to-head comparisons are not available. This meta-analysis reports only the absolute IOP-lowering effects per study for 9 AM, 11 AM, 4 PM, and the mean daytime curve. The relative IOP decrease (related to the baseline IOP) would have been of clinical interest as well. Furthermore, the differences between 2 study drugs are pooled, but the IOP decreases for each of the study drugs are not reported. Thus, here one knows the differences between drugs, but no information is provided for the relative IOP-lowering effect of a PTFC. Figure 2 is useful in illustrating one of the key issues in this field of research: many studies have been conducted, but only a few address the issue of a head-to-head comparison.

As always, with scientific evidence, the interpretation of this comprehensive meta-analysis is limited by certain factors. Although it was a network meta-analysis no indirect comparisons were used. Network meta-analysis (or multiple treatment meta-analysis) is an extension of the meta-analysis methodology to more than 2 comparisons (20, 21). It can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable by indirect comparisons (i.e., by contrasting the treatments of interest with a common reference and deducing their relative effects). Further, there needed to have been a better description of the included papers with respect to the study design. For instance, in some of the studies, treatment naive patients or treated patients after a washout period were included. In other studies, however, a run-in design on timolol was employed. In both situations, it is possible to draw conclusions on the total IOP lowering of the PTFC; however, several issues arise. One issue is how omitting the second timolol dose after a timolol twice daily run-in period and switching to a PTFC administered once daily is handled. The second issue is whether an IOP-related response criterion after a run-in period is included in case of a run-in design. This is of importance since one does not want to include timolol non-responders in these studies.

It is logical with fixed combinations that are administered morning or evening to document the time point of administration (am or pm). Certainly, if one is interested in the real efficacy of PTFCs it is essential to include as many time points as possible evenly distributed through the peak and trough periods when comparing these drugs. A few of the individual studies of this meta-analysis employed a more rigorous IOP evaluation protocol (i.e., when a complete 24-hour IOP curve was performed). Consequently, by including only 3 measurements (9 AM, 11 AM, and 4 PM time points), one misses important data that better delineate the extent of IOP lowering throughout the peak and trough efficacy periods.

Meta-regression analysis could also be performed for potential factors causing heterogeneity, such as run-in treatment, timing of treatment, treatment duration, type of trial design parallel vs cross-over design, and number of IOP time points (22).

Extrapolating from their evidence the authors suggest greater efficacy for the bimatoprost-timolol fixed combination compared with the latanoprost-timolol and travoprost-timolol fixed combinations.

This conclusion should be interpreted with some caution since the direct comparisons between these fixed combinations showed considerable heterogeneity (I^2=97.6% at 9 am, 97.8% at 11 AM and at 4 AM, and 96.8% for the mean diurnal curve). Further, the direct comparison between bimatoprost-timolol and travoprost-timolol fixed combinations is based on a single study (23) in which patients who responded inadequately to the latanoprost-timolol fixed combination were switched to either bimatoprost-timolol or travoprost-timolol fixed combination therapy. This study introduces significant clinical heterogeneity. Study patients are, to a certain extent, suboptimal responders to timolol, latanoprost, or the latanoprost-timolol fixed combination.

The current meta-analysis by Aptel et al demonstrates that the 3 available PTFCs provide greater IOP reduction at all time points and a lower prevalence of conjunctival hyperemia than the 3 individual prostaglandin monotherapies. The impact of this conclusion in real-life clinical practice is important. It suggests that PTFCs are more effective and better tolerated, so they should be preferable to individual prostaglandin constituents when further IOP lowering is needed. It is likely that in real life the impact of these fixed combinations may be greater: better IOP control, less adverse events, and better adherence. Although these suggestions are reasonable, direct evidence has not been provided for these as yet. The current meta-analysis contradicts the conclusions of the NICE meta-analysis, which reported only a small (0.3 mmHg) difference between PTFCs and prostaglandin analogues (24; Fig. 27, Appendix E). It should be noted that the results of this meta-analysis were made available on the Web, but were never published in a peer-reviewed journal. Importantly, the NICE meta-analysis needs updating since several trials on PTFCs have been conducted and published since 2008 and even combined through meta-analysis (25-27). With regard to information sources used, it did not report the use of supplementary approaches to identify studies, such as hand searching of journals, checking reference lists, searching trials registries or regulatory agency Web sites, contacting manufacturers, or contacting authors. Furthermore, in the databases searched there were no dates of coverage, or the dates last searched.

In order to make appropriate decisions about new agents, evaluation of the wider perspective, including unpublished studies, is required (16). Only 3 studies were eligible according to the strict inclusion criteria of 6 months follow-up employed by the NICE meta-analysis (24) and of those only 2 compare a single PTFC to monotherapies (28, 29). Instead of limiting the meta-analysis to studies with longer follow-up, it would have been more clinically relevant to include studies with shorter follow-up to see whether the results of studies with shorter follow-up were different from the few studies with longer follow-up through subgroup analysis or meta-regression analysis.

There may be a fundamental flaw in the selection process of the NICE meta-analysis. The basic assumption that since glaucoma is a lifelong disease only long-term clinical trials should be included largely depends on the question asked. If the clinical question in the meta-analysis was whether IOP lowering is effective in managing glaucoma and reducing progression then longer term studies are clearly needed. But if the question is whether PTFCs are safe and effective then all pertinent studies should have been included. The 2 studies that qualified for the NICE meta-analysis only really compare the efficacy of the latanoprost/timolol fixed combination versus latanoprost and timolol monotherapies (28, 29).

Further, it is important to emphasize that the design of these two studies tends to minimize the difference between the latanoprost/timolol fixed combination and latanoprost. For example, in the study by Higginbotham et al (29), a run-in period on timolol administered twice daily was followed by 3 study arms: continuation of timolol, switch to latanoprost administered in the evening (20:00), or switch to the latanoprost/timolol fixed combination administered in the morning (08:00). The IOP measurements were taken at 08:00, 10:00, and 16:00. This design underestimated the efficacy of the PTFC given in the morning compared to latanoprost dosed in the evening. It was demonstrated by Alm and Stjernschantz (30) in a 3-month crossover trial that there is a statistically significant difference between latanoprost administered in the evening (–8.6 mmHg, 35%) and latanoprost administered in the morning (–7.8 mmHg, 31%) ($p<0.001$).

This meta-analysis clearly summarizes the evidence from available clinical trials and indirectly reflects what is published in individual studies and also what every clinician experiences in real-life practice. Importantly, the results achieved to date employing a meta-analysis are highly dependent on the range and quality of studies included. It is relevant here to emphasize that the chain of a meta-analysis is as strong as the weakest individual randomized controlled trial. Striving for both statistical and clinical homogeneity and correctly matching study designs is important. Future head-to-head studies that assess the true efficacy of PTFCs over a 24-hour period may eliminate inconsistencies arising from key issues discussed before (selection of time points measuring the IOP, time of administration relative to the peak and trough efficacy of the fixed combination). There is much scope for further research into the assessment of adherence and other advantages (tolerability) with PTFCs versus concomitant unfixed therapies. Finally, there is a major need to study the optimum treatment strategies with fixed combinations in children.

Fixed combination drugs like the PTFCs can provide effective IOP control, enhance adherence and convenience, eliminate the washout effect, and significantly reduce exposure to preservatives. In real-life practice PTFCs can of-

ten 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 them. As yet, there is no information on whether all fixed combinations improve long-term clinical outcome and this will be a promising line of future research. The possibility exists that PTFCs may prove instrumental in improving management and prognosis in glaucoma.

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