Re: Singh et al.: Nepafenac 0.3% after cataract surgery in patients with diabetic retinopathy: results of 2 randomized phase 3 studies (Ophthalmology. 2017;124:776-785)

TO THE EDITOR: We read with great interest the recent examination by Singh et al of nepafenac 0.3% for the prevention of postoperative macular edema (PME) in patients with diabetic retinopathy undergoing cataract surgery.1 This report consisted of results from 2 substudies. Substudy 1 showed statistically significantly better visual outcomes in those on nepafenac; substudy 2 failed to reach many of the same results. This finding is similar to 2 parallel studies of nepafenac 0.1% in patients with diabetic retinopathy undergoing cataract surgery where both studies found anatomic benefit,2,3 but one did not show significant visual benefit.2 The presence of conflicting visual results may indicate that topical nonsteroidal anti-inflammatory drugs (NSAIDs) may not benefit all subgroups of patients with diabetic retinopathy. There was 1 treatment/nepafenac group and 1 vehicle group in each of the subgroups of patients with diabetic retinopathy.1

With enough follow-up, the difference between the groups may narrow further and reach equality. This finding is similar to 2 parallel studies of nepafenac 0.1% in patients with diabetic retinopathy undergoing cataract surgery where both studies found anatomic benefit,2,3 but one did not show significant visual benefit.2 The presence of conflicting visual results may indicate that topical nonsteroidal anti-inflammatory drugs (NSAIDs) may not benefit all subgroups of patients with diabetic retinopathy. There was 1 treatment/nepafenac group and 1 vehicle group in each of the sub-studies by Singh et al.1 Between these 4 total groups (divided across 2 substudies), the vehicle group in study 1 stands out as having markedly worse outcomes. The authors indicated that a more in-depth analysis, not presented within the paper, could not explain the disparities between the substudies.1 Risk factors for PME include a prior history of treatment for diabetic macular edema, noncentral macular edema preoperatively, and intraoperative anterior vitrectomy, and as such expanded comparisons by Singh et al1 comparing these factors between treatment arms as well as studies 1 and 2 may be insightful given the discordant visual outcomes.

The clinical significance of the presented outcomes is worth considering. Although mean change in best-corrected visual acuity and central subfield macular thickness were statistically significantly better in the treatment group, the magnitude of change was modest and may not be as clinically significant (see Figures 7 and 8 in the original article).1 By day 90, the differences between the groups had narrowed. Singh et al1 found improvement in mean best-corrected visual acuity from baseline was greater in the nepafenac group including at day 7 (P = 0.088) and day 14 (P < 0.05), which is earlier than the typical time-frame for PME. The mean change in central subfield macular thickness was less in the treatment group at all time points (even at days 7 and 14); however, the mean change in central subfield macular thickness in the nepafenac group gradually increased during the study, whereas the vehicle group’s peaked between 30 and 60 days and then decreased. With enough follow-up, the difference between the groups may project to narrow further and reach equality. This finding is especially noteworthy, because the peak risk for diabetic macular edema was recently noted to occur 3 to 6 months after cataract surgery4—follow up by Singh et al1 ends just as the greatest risk of diabetic macular edema may be emerging, which could complicate the picture.

Presumably, patients who developed visually significant macular edema during the study by Singh et al1 received treatment and the outcomes of these patients is an important consideration. If their acuity returned to premacular edema levels, then the development of PME had limited practical consequences. It would be important to know how visual acuity data were analyzed in those who developed macular edema—was the vision after treatment of macular edema considered (i.e., “intent to treat” based on initial randomization) or was last observed vision at the time of macular edema diagnosis carried forward? If it was the latter, the results may not be representative of outcomes in clinical practice.

The findings by Singh et al1 also conflict with the results of a large retrospective real-world study, where topical NSAIDs showed no effect in patients with diabetic retinopathy undergoing cataract surgery (n = 11 579).5 This study used propensity score matching for multiple ocular and systemic factors to emulate randomized clinical trials in estimating the average treatment effect.

Finally, PME is often mild, responds well to treatment, frequently resolves without intervention, and does not have significant long-term visual consequence for most patients.3 The question remains: What is the clinical and practical usefulness of preventing a condition that is easily treatable and has limited long-term visual consequence? Knowing the long-term visual outcomes in the patients reported by Singh et al may be more helpful in determining if prophylactic NSAID use has enduring value. Future investigations should delineate which patients achieve the greatest long-term benefit to topical NSAID prophylaxis. We congratulate Singh et al1 on their insightful and informative study.

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References


