Correspondence

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

TO THE EDITOR: We read the article published by Singh et al1 with great interest. However, we believe that some discussion is required. The authors present results of 2 studies assessing clinical benefits of nepafenac 0.3% over vehicle in reducing the risk of pseudophakic cystoid macular edema (PCME) in phacoemulsification cataract surgery.

In the methodology section, the authors evaluate the severity of diabetic retinopathy (DR) on fundus photographs obtained at the screening visit as follows: no apparent retinopathy, mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). However, it is unclear whether patients with no apparent retinopathy and PDR were excluded from the study. And, if PDR patients were excluded, shouldn’t the title of the paper clearly manifest that the results refer to NPDR only?

The risk factors of PCME have been recently assessed by Chu et al2 in a large, retrospective database study of 81 984 surgeries. Eyes of patients with diabetes carried an increased relative risk, which increased proportionately with the severity of DR. Thus, it seems justified to ask whether the authors attempted to find differences between the outcomes in terms of DR severity. This issue has a significant translation into the expected outcome. Modjtahedi et al3 conducted a multicenter retrospective analysis based on 11 579 patients demonstrating that therapeutic response to topical nonsteroidal anti-inflammatory drugs (ketorolac in 72.4% of the cases) and glucocorticoids (prednisolone in 96.2% of the cases) may vary depending on the severity of DR. Although the treatment was shown to be effective in prevention of PCME in nondiabetic subjects (relative risk, 0.68; 95% CI, 0.58–0.72) and in diabetic patients without retinal complications (relative risk, 0.51, 95% CI, 0.32–0.82), it did not produce expected therapeutic benefits in DR group (relative risk, 1.06; 95% CI, 0.81–1.38). Moreover, Friedman et al4 analyzed the efficacy of nepafenac 0.1% in management of non–center-involved diabetic macular edema (DME). One year of topical therapy (3 times a day) did not result in a significant reduction of the edema. These findings imply that cyclooxygenase products may play only a marginal role in the pathomechanism of DME.

Figure 4 in the original article presents a bar graph showing the percentage of patients with best-corrected visual acuity improvement through day 14 and maintained through day 90. Major differences between the results of studies 1 and 2 are presented, with no statistical difference between nepafenac and vehicle in study 2. Did these studies differ in the methodology? Figure 7 presents a graph showing the mean change in best-corrected visual acuity from preoperative baseline to each visit in patients treated with nepafenac 0.3% and vehicle in each study, and in the pooled analysis (full analysis set). However, were there any statistically significant differences between the groups in consequent follow-up visits, particularly in study 2?

The empirical data were analyzed thoroughly and with piety. Readers will certainly—as we did—appreciate the authors’ endeavor. However, one could feel unsatisfied when juxtaposing results that spring from the 2 international studies. The rift found is remarkable. The authors mention some post hoc subgroup analyses that aim at identifying the factors (or confounders) that potentially may have confused the issue. In that context, we would like to encourage the authors to carry out, once more, a more in-depth analysis of the underlying problem(s). Please consider, for example, a stepwise regression model, multilevel modeling, and a mixed-effects design. Estimates obtained from the aforementioned “fashion” will enrich the results to date and most likely will help to find a factual (and backed up by evidence) explanation for the discussed big discrepancies between the 2 presented studies. We look forward to solving the riddle.

Finally, we believe that evaluating PCME only on the basis of foveal thickness might be inaccurate. It was shown that significant differences in edema morphology in DME and PCME exist.5 In DME, the pattern of edema might be asymmetric, owing to focal leakage, cysts are localized mainly within the outer nuclear layer/Henle’s layer cysts, presence of hard exudates, microfoci, and disruption of the photoreceptor layers is observed. In PCME the edema has a central pattern with subretinal fluid and intact hyperreflective bands.

Was any attempt to assess morphologic changes performed?

ANDRZEJ GRZYBOWSKI, MD, PhD1,2
PIOTR KANCLERZ, MD, PhD3

1Department of Ophthalmology, Poznan City Hospital, Poznan, Poland; 2Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland; 3Department of Ophthalmology, Medical University of Gdansk, Poland

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Correspondence:
Piotr Kanclerz, MD, PhD, Department of Ophthalmology, Medical University of Gdansk, ul. Smoluchowskiego 17, 80-952 Gdansk, Poland. E-mail: p.kanclerz@gumed.edu.pl.

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