Correspondence

Randomized, Controlled, Phase 2 Trial of Povidone-Iodine/ Dexamethasone Ophthalmic Suspension for the Treatment of Adenoviral Conjunctivitis

EDITOR:

WE CONGRATULATE PEPOSE AND ASSOCIATES[1] ON THEIR recent article but note that povidone-iodine/ dexamethasone ophthalmic suspension is not commercially available. Pepose and associates[1] did not mention how this combination was prepared. There is also no mention of the details of the vehicle. Punctate keratitis and subepithelial infiltrate may develop between 6 and 13 days from the onset of the disease and may last for months.[2] Therefore, a follow-up period of 12 days as evaluated by Pepose and associates[1] is too short to evaluate the long-term effects of the drug on the resolution of these lesions. Steroid responders, people with a history of glaucoma, and those with intraocular pressure >21 mm Hg were excluded from the study. However, Pepose and associates[1] have not measured intraocular pressure during the course of the study or in the long term. This raises our concern on the safety profile of the treatment. Their study requires long-term follow-up with a clearly defined control arm before applying the conclusion of the study in our daily clinical practice.

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Cataract Surgery and Rate of Visual Field Progression in Primary Open-Angle Glaucoma

REPLY

WE THANK TUUMINEN AND GRZYBOWSKI FOR THE INTEREST IN our recent article[1] and welcome the opportunity to address their comments.

We agree with Tuuminen and Grzybowski that postoperative transient intraocular pressure (IOP) spikes are common (up to 50% of cases) and potentially harmful events in patients with glaucoma who are undergoing cataract surgery, and we certainly agree that appropriately diligent intraoperative and postoperative surveillance is essential in these patients.[2] Several risk factors have been associated with postoperative IOP spikes in patients with glaucoma, including high preoperative IOP, pseudoexfoliation syndrome, incomplete removal of viscoelastic material, scleral-corneal incision (vs clear corneal incision), inexperienced surgeons, and complicated cases.[2] Our study population was at low risk for postoperative IOP spikes because most of the previously mentioned risk factors were set as exclusion criteria, and all the surgery and postoperative management was performed by an experienced anterior segment surgeon (J.C.). Only 9.8% and 17.4% of eyes had an IOP ≥30 mm Hg or a rise of ≥10 mm Hg on the first postoperative day. Although a postoperative IOP spike might have contributed to the worsening of the visual field (VF) rates, its contribution was likely negligible. Briefly, two main reasons supported this hypothesis: 1) the VF worsening continued over many years after the surgery; and 2) the postoperative VF rates were nearly unchanged in the early postoperative years, and deterioration began years after the surgical intervention. This issue was extensively discussed in our paper.

Tuuminen and Grzybowski argued that the extended follow-up of our retrospective study could have introduced a statistical bias. Glaucoma is a chronic disease, and we believe that the long-term nature of this study is a strength rather than a limitation.

Tuuminen and Grzybowski argued that "more than one visual field device" was used in our study, but this is not true because all VF tests were performed with a Humphrey Visual Field machine (and all IOP readings were measured with Goldmann applanation tonometry). They perhaps meant that VF examinations were obtained with either 30-2 or 24-2 Swedish Interactive Threshold Algorithm standard strategy, but, as detailed in our paper, only the 54 locations of the 30-2 pattern corresponding to the 24-2 test pattern were included in the pointwise analysis. Although global index rates might

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slightly vary between 30-2 and 24-2 patterns, this is not the case for the pointwise-based methods. Regardless of the method that was used, all results pointed toward an acceleration of VF decay rates in the postoperative period.

Tuuminen and Grzybowski speculated that other nonglaucomatous phenomena, such as posterior capsule opacification (PCO), could explain the faster VF decay rates in our study population. We acknowledge that the postoperative degree of posterior capsule clarity (as well as the preoperative degree of cataract) were not included in our study. Although both these events reduce the VF sensitivity globally and may affect the mean deviation rate, we also found similar results with the VF index rate and glaucoma rate index (GRI), which are more robust against generalized VF depression (Rabiolo A et al, American Academy of Ophthalmology Annual Meeting; 2018; Chicago).[3] Also, mean visual acuity at postoperative month 3 did not significantly decrease over the follow-up up to postoperative year 5 ($P = .72$). Taken together, all these findings did not support a significant role for PCO in the postoperative VF decay.

Tuuminen and Grzybowski wondered why the number of medications decreased in the postoperative period despite the worsening of VF rates, and asked whether decisions were based solely on IOP readings. All the therapeutic decisions were made on an individual basis by the clinician treating the patients (J.C.), taking into account many factors, including glaucoma severity, VF decay rates, structural progression, status of the fellow eye, life expectancy, patient preferences and compliance, and presumed target IOP.

Tuuminen and Grzybowski suggested that "non-linear glaucoma progression should be incorporated in the statistical analysis to avoid the overestimation of VF decay postpseudophakia." They should note that 1 of the methods (GRI) used in this study to measure VF decay rates was based on pointwise exponential regression, which takes into account the nonlinear VF decay.[4]

Tuuminen and Grzybowski wondered whether quantitative optical coherence tomography (OCT) data confirmed the postoperative worsening found at the VF analysis. Due to the long-term follow-up of this study, patients were imaged with different OCT devices due to technological evolution. Inability to compare data acquired with different instruments (or even different releases of the same device) is a bothersome limitation of OCT imaging for long-term follow-up in glaucoma.[5] One would expect differences between structure and function because disagreement between structural and functional rates of progression were extensively demonstrated.[6] Further studies are warranted to investigate the effect of cataract surgery on rates of structural decay.

We appreciate the suggestion of the Tuuminen and Grzybowski to look at the effect of different intraocular lenses (IOLs) on the VF examination, but this is completely outside the scope of our study. Although different IOLs may have a slight effect on visual sensitivity, they are not likely to have an impact on rates of progression.

We appreciate the opportunity to further elaborate on the methodology and results of our study.

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Effects of Crocin on Diabetic Maculopathy: A Placebo-Controlled Randomized Clinical Trial

EDITOR:

I READ WITH GREAT INTEREST THE STUDY ENTITLED "EFFECTS of crocin on diabetic maculopathy: A placebo-controlled randomized clinical trial," by Sepahi and associates,[1] which evaluated the effects of crocin as a supplement on reducing inflammation in patients with diabetic maculopathy. The authors concluded that administration of 15 mg oral crocin could be effective on diabetic macular edema (DME) and significantly decrease central macular thickness and improved visual acuity compared to the placebo group. I would like to address several issues related to the aforementioned study by Sepahi and associates.

Although the pathogenesis of diabetic retinopathy (DR) has not been completely elucidated, accumulating evidence suggests that the inflammatory reactions may play a major role. Microglia are the primary innate resident immune cells in the retina that are involved in the inflammatory changes causing DR.[2] It has been reported that under diabetic conditions, microglia cells become activated, migrate near the perivascular areas, and upregulate the expression of several inflammatory cytokines, including