Correspondence

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

REPLY

WE WOULD LIKE TO THANK RAMAKRISHNAN AND ASSOCIates for their comments and welcome the opportunity to respond to the points made in their letter.

To address the first point regarding preparation of the treatments, the formulation of the study treatment povidone-iodine (PVP-I)/dexamethasone (DEX) was composed of the 2 actives PVP-I and DEX and other excipients approved for use in ophthalmic formulations. The vehicle control had a similar composition as PVP-I/DEX without the actives, and a commonly used preservative was added to the vehicle. This preservative was not included in PVP-I/DEX since PVP-I enables the product to be self-preserving. Ramakrishnan and associates raised concerns that the follow-up period of 12 days in our study[1] was too short to evaluate the potential long-term effects of PVP-I/DEX on the resolution of punctate keratitis and subepithelial infiltrates. Our study was a phase 2 proof-of-concept clinical trial designed to include subjects with the signs and symptoms of adenoviral conjunctivitis and was not limited to a specific subset of subjects with punctate keratitis and subepithelial infiltrates. Adverse events, whether related to the study treatments or not, were assessed during the study visits in all patients. As shown in Table 3 of our article, the rates of these corneal adverse events in the PVP-I/DEX group were comparable to those in the vehicle group.[1] Although it was not stated in the article, all patients with corneal adverse events were followed, and a relationship to the study drug in any treatment group was not suspected for any corneal adverse event.

Ramakrishnan and associates also questioned why we did not measure intraocular pressure (IOP) during the study. In previous studies where ophthalmic DEX 0.1% was administered alone[2] or in combination with PVP-I[3] for 7 days, and IOP was measured, treatment with these drugs did not lead to an elevation in IOP. The label warning for the approved DEX product Maxidex (0.1% DEX ophthalmic suspension)[4] states that IOP should be routinely monitored if the product is used for ≥10 days. We did not measure IOP in our study since the PVP-I/DEX was administered for 5 days only. In response to the final point raised, this was an early phase 2 study. Development of this product for approval will adhere to the required regulatory path with appropriately controlled studies using agreed-upon posology, duration, and follow-ups. Phase 3 clinical trials are ongoing (NCT02998541 and NCT02998554).

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CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article for any disclosures of the authors. Dr Narvekar and Dr Haque were employees of Shire (Lexington, Massachusetts, USA) at the time the original study was conducted.

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

WE HAVE READ WITH GREAT INTEREST THE ARTICLE BY KIM and associates.[1] Cataract surgery is regarded especially beneficial in glaucoma patients based on its potential in attenuating intraocular pressure (IOP) and improving visual field (VF) reliability and optic nerve head and nerve fiber imaging quality. However, cataract surgery in patients with glaucoma requires diligent peri- and postoperative care.

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Interestingly Kim and associates presented that the rate of VF progression was higher in the follow-up period after cataract surgery than in the period before the surgery. Furthermore, eyes with worse baseline VF defect and those without prior trabeculectomy were concluded to be more vulnerable to intraoperative and early postoperative stress caused by cataract surgery. The postoperative peak of IOP was associated with postoperative rates of VF decay.

In this study, the baseline IOP was relatively low both in mild and moderate-to-severe primary open-angle glaucoma (POAG) patients. It should be noted that intraoperative and early postoperative IOP spikes may outweigh statistically significant but clinically marginal long-term IOP reduction in terms of glaucoma progression.[2] In light of the findings, proper phaco settings and the type of ocular viscosurgical device (OVD) and its careful removal at the end of the surgery, as well as efficient postoperative antiglaucoma medication, are of special importance. These findings also raise the question whether prostaglandin analogs are advisable to pause before and after cataract surgery in glaucoma patients (especially in ones with VF defects), or not.[3]

Given the long pre- and postoperative follow-up time (median 6.5 and 5.3 years, respectively) a retrospective study design predisposes the data for statistical challenges and bias when the results are not properly adjusted for confounders. First, the long follow-up predisposes the risk of changing habits not recognized. For instance, there was more than 1 visual field device. Was one of the devices used toward the starting date of the study rather than at the end of the study period, and were the settings similar over the follow-up? The same comes with IOP measurements. Were the IOP measurements based on applanation or rebound tonometry, or both? And were some of the devices used toward the starting date of the study? Interestingly, during the follow-up, increased rates of glaucoma progression according to visual fields were noted, but the mean number of glaucoma meds were reduced. Were the treatment decisions based on the IOP readings, or is the discrepancy explained by something else, such as compliance problems when patients are getting older? This in turn raises a question: Did automated imaging analysis of the glaucoma (OCT, GDX, etc) support the findings regarding VF decay? Second, considering the long follow-up time, the results should be adjusted with ocular comorbidities such as posterior capsule opacification (PCO) in pseudophakic eyes. Considering the potential differences in the IOL optics (eg, light-filtering qualities), the analysis between clear and blue light–filtering intraocular lenses would have been informative. Third, although the associations between the baseline patient age and visual field rates after the surgery were nonsignificant, the long follow-up periods pre- and postoperatively and nonlinear glaucoma progression should be incorporated in the statistical analysis to avoid the overestimation of VF decay post-pseudophakia.

Taken together, the findings presented by Kim and associates need to be confirmed in a controlled prospective study setting. To evaluate the role of intraoperative and early postoperative stress on VF decay, one could randomize the patients to different peri- and early postoperative glaucoma treatment protocols, phaco settings and fluidics, as well as conduct a subgroup analysis according to the presence of early IOP spikes. Polyclinical evaluations could be supplemented by the IOP home device measurements.

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Risk Factors Associated with Persistent Anterior Uveitis After Cataract Surgery

EDITOR:

THE UVEITIS OF CATARACT SURGERY HAS RECENTLY BEEN studied by Reddy and colleagues.[1] They report that the uveitis is typically of a longer duration in African Americans than in whites. It is also stated that any anterior uveitis that persists "may not be detrimental to long-term visual outcomes."

Persisting uveitis after cataract emulsification merits some thought. While such uveitis may not adversely affect persons of African ancestry, in older whites it may trigger a neovascular effect at the macula. Degeneration of the aged macula is common in white populations. It has been debated whether cataract surgery can convert age-related macular degeneration (AMD) from the dry to the wet