Endothelial Cells Count: The Importance of Monitoring Corneal Endothelium When Approving New Ocular Medications and Devices

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Topical intraocular pressure-lowering medications are the mainstay of glaucoma treatment. Although we are fortunate to have multiple classes of drugs available to us, no new classes had been developed for roughly 2 decades before netarsudil 0.02% (Rhopressa; Aerie Pharmaceuticals, Inc, Irvine, CA) was approved in late 2017. The ROCKET-2 (Rho Kinase Elevated IOP Treatment trial 2) was a prospective, multicenter, double-masked, randomized, active-controlled phase 3 clinical trial that compared netarsudil 0.02% once daily, netarsudil 0.02% twice daily, and timolol 0.5% twice daily for 12 months. In this issue of *Ophthalmology Glaucoma*, Mundorf et al (see page 421) report the findings from a post hoc analysis conducted on 386 of the ROCKET-2 patients after 3 months of treatment to compare the effects of netarsudil and timolol on corneal endothelial density and morphologic features. What became evident during the review process of this article was that perhaps not all glaucoma specialists may be aware of why such a post hoc analysis was conducted during the pivotal phase 3 clinical trials.

It is well recognized that endothelial cells (ECs) are critical to maintaining the clarity of the cornea and that they have little regenerative potential. As soon as they are damaged and lost, they do not self-repair. Although as Mundorf et al correctly point out, preclinical animal and ex vivo data suggest that Rho-Kinase inhibitors (ROKi) may have EC regenerative capabilities. However, as was noted during our review, this was neither the purpose nor the correct design to assess that hypothesis.

The preservation of ECs is particularly important as we age given that EC density (ECD) steadily decreases with age. For our glaucoma patients, this loss may be compounded by elevated intraocular pressure, inflammation, exfoliation, comorbid corneal pathologic features like Fuchs disease, cataract and glaucoma surgeries, including tube shunt and laser procedures. A review of the effect of glaucoma surgeries on ECs showed that Ahmed (New World Medical, Rancho Cucamonga, CA), Molteno (Molteno Ophthalmic Limited, Dunedin, New Zealand), and Baerveldt (Johnson & Johnson, Santa Ana, CA) glaucoma implants all caused at least 10% ECD loss over just 12 months.

Given the recent recall of the Cypass Micro-Stent (Alcon Laboratories, Inc, Fort Worth, TX) because of the postmarketing surveillance of ECD, we have all become that much more aware of the possible impact our glaucoma treatments can have on corneal health. Traditionally, the United States Food and Drug Administration (FDA) has not required monitoring of EC counts for the approval of implantable devices, including intraocular lenses. However, many patients benefited from these devices, and it would not be unreasonable to consider long-term EC loss to be of secondary importance when the patient’s vision loss has progressed to the point of requiring major glaucoma surgery.

The same calculation may not hold for microinvasive glaucoma surgeries, which demand a much higher safety profile, but continue the tradition of not requiring EC counts. In fact, the pivotal study used as the basis for the FDA approval of the first of these devices, the iStent Trabecular Micro-Bypass Stent (Glaukos, San Clemente, CA), does not even mention ECs. The clinical trials for more recent microinvasive glaucoma surgery devices are now monitoring ECD; however, the follow-up periods are relatively short. The iStent Inject (Glaukos), Hydrus Microstent (Ivantis, Irvine, CA), Xen Gel Stent (Allergan, Irvine, CA), and the CyPass Micro-Stent were all approved by the FDA after 2 years or less of clinical follow-up data. In fact, the CyPass Micro-Stent is the only microinvasive glaucoma surgery device with more than 3 years of follow-up data with EC counts. Notably, it is only in years 4 and 5 that we see a statistically significant difference in ECD between the CyPass and control patients.

Despite these findings, new ocular drugs and devices often are approved with 2 years or less of clinical data. Dexycu (EyePoint Pharmaceuticals, Watertown, MA), a dexamethasone intraocular suspension for postsurgical inflammation, recently was approved after just 90 days of follow-up data. During this period, no statistically significant difference in EC loss between the treatment group (−13.59 ± 1.48%) and the topical steroid control group (−12.04 ± 2.29%) was found.

Early this year, Durysta (Allergan), a bimatoprost implant, was approved after a 24-month phase 2 clinical trial. Their initial results showed a negligible difference between the mean central corneal ECDs in the study eyes (2638 ± 206 cells/mm²) and fellow eyes (2650 ± 222 cells/mm²) at 6 months. However at 2 years, the data showed a clear trend toward decreased ECDs in the study eyes.
(2607.0 ± 203.0 cells/mm$^2$) compared with fellow eyes (2651.6 ± 196.4 cells/mm$^2$). This reflects a mean decrease of 88.9 ± 135.3 cells/mm$^2$ in the study eyes and of 22.2 ± 127.8 cells/mm$^2$ in the fellow eyes. This suggests that an increased rate of EC loss occurs in the treatment eyes. Because of these risks, the recommendation is that Dursysta be “limited to a single implant per eye without retreatment.” Further studies with longer follow-up will be needed to determine whether these intraocular implants have an increasingly significant effect over time.

The FDA, in reviewing ocular drug and device applications, considers EC health an important factor in the evaluation of an application. Although no current FDA regulation exists, all new drugs need to evaluate their effect on ECD and morphologic features. In general, current topical glaucoma medications are not considered to cause loss of corneal ECs. Most studies, including the Ocular Hypertension Treatment Study with 6 years of follow-up, did not find a decrease in ECD with glaucoma medications.

Overall, Mundorf et al\textsuperscript{1} conclude that 3 months of treatment with 0.02% netarsudil shows similar effects on the corneal endothelium as timolol 0.5% twice daily in patients with relatively healthy corneas and healthy pachymetries. They appropriately included ECD, percentage of hexagonal cells, and the coefficient of variation in their results. Endothelial cell density is a direct measure of the number of ECs in a given area of cornea, with 300 to 500 cells/mm$^2$ required to maintain deturgescence. The coefficient of variation reflects the variation in EC size, and percentage of hexagonal cells is a measure of variation in cell shape, both of which may be a more sensitive measure of EC health than ECD.\textsuperscript{11}

What we do not know from these studies is the long-term effect, especially in those individuals requiring more complicated and complex glaucoma treatment, those taking multiple intraocular pressure-lowering products, those who already have compromised ECs, or those who fall into any combination of the above categories. It remains important for us as clinicians to be vigilant in our own postmarketing surveillance as we introduce these novel glaucoma drugs and devices into our practice. We await future reports on more long-term outcomes from topical netarsudil and others, as well as more formal FDA guidance.

Footnotes and Financial Disclosures

Financial Disclosure(s): The author(s) have made the following disclosure(s): B.M.W.; Consultant — Guidepoint/EyeGate; Board member — Glaucomix; Co-founder — Qlaris.

References


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