Corneal Graft Survival and COVID Vaccines

As more patients are vaccinated against COVID-19, cornea surgeons are encountering a late postoperative complication that heretofore has been rare: postvaccination corneal allograft rejection.

The first publication of case reports came in April, from clinicians at Moorfields Eye Hospital in London. Prior to that, anecdotal reports of COVID vaccine–associated rejection episodes began surfacing during the first few months of 2021, and some of these likely will be the subjects of additional peer-reviewed papers this year, said Bennie H. Jeng, MD, at the University of Maryland School of Medicine in Baltimore.

“This is an issue around the world,” Dr. Jeng said. “On the Keranet listserv of the Cornea Society, more and more cornea surgeons are reporting this with the COVID vaccinations.”

Need for ongoing vigilance. Maria Phylactou, MD, who coauthored the Moorfields paper, and Dr. Jeng agreed that it is important for ophthalmologists in the COVID era to be vigilant for this. Even eyes that have been doing well for years following a transplant can be affected, so patients should be alerted to watch for rejection signs, they said.

“What we’d like to highlight is, first, that this is a very rare event, but it definitely can occur—and second, that early recognition and early intensive treatment are essential,” Dr. Phylactou said.

Case examples. The first affected patient at Moorfields had a successful, unilateral keratoplasty with full graft attachment, a clear cornea, and best-corrected visual acuity (BCVA) of 6/6 (20/20) at postsurgical day 7. Fourteen days after the transplant, she received the first injection of the Pfizer-BioNTech vaccine. A week later, her VA decreased, and she developed other signs of acute rejection.

The second patient had bilateral grafts that had been functioning well for six years and three years. Three weeks after her second dose of the Pfizer-BioNTech vaccine, she presented with acute graft rejection in both eyes.

Treatment consisted of one week of hourly dosing with corticosteroid eyedrops (dexamethasone), followed by judicious tapering. Both patients recovered their previous visual acuity, the researchers reported.

An issue of timing? Although a causal link is not proven, the timing of vaccination and development of rejection signs suggested to Dr. Phylactou and her colleagues that the patients’ immune responses might have been injuring the inner surface of the donor corneal tissue, she said.

“In the first case, you could see the rejection happen very quickly, at the time when the immune system would be responding to the vaccine. In the second case, the patient had a serious reaction bilaterally, which is extremely rare, considering that she had a different donor for each eye. So that makes the probability of a causal association with the vaccination even higher,” she said.

Dr. Jeng noted that in the cases that he has heard about anecdotally, rejection seems to occur one to two weeks after the second vaccine dose, which suggests the body’s immune response is the culprit. “That makes sense, right? Because the second shot is the one exposing the patient to the antigens that the body is seeing for the second time,” he said.

Not a brand-new issue. The literature contains a few reports over the last three decades of vaccine-related graft rejection, Dr. Jeng said. He is a coauthor of a study slated to be published...
in *Cornea*; when he and his colleagues surveyed cornea surgeons before the pandemic, they found that a fifth of the respondents had seen rejection associated with herpes zoster or influenza vaccines.²

**Advice to patients.** Neither Dr. Phylactou nor Dr. Jeng would discourage patients from getting the COVID vaccine. However, postponing nonurgent keratoplasties until a few months after vaccination might be worthwhile, they said. If this is not possible, patients should be advised to seek treatment early if signs of rejection occur, they said. And those with existing corneal grafts also should be reminded of this, Dr. Jeng added. —Linda Roach


**RESEARCH**

**RETINA**

**Biosimilar Drug for AMD Shows Promise**

**THE BIOSIMILAR OPHTHALMIC DRUG** FYB201 (bioeq/Formycon) is clinically equivalent to ranibizumab for treating neovascular age-related macular degeneration (AMD), an international team of researchers has reported.¹

“The study showed noninferiority between the biosimilar FYB201 and the reference product, ranibizumab,” said coauthor Peter K. Kaiser, MD, at the Cleveland Clinic’s Cole Eye Institute. He added, “Biosimilars are different from generic medications and require different regulatory hurdles. However, the study did show noninferiority, which would suggest similar efficacy.”

**Study specifics.** For the prospective phase 3 study, treatment-naive patients with wet AMD were evaluated at centers in 12 countries. Participants were randomized to receive monthly injections of either FYB201 (n = 238) or 0.5 mg ranibizumab (n = 239).

At 48 weeks, data were available on 199 patients who had received FYB201 and 189 in the ranibizumab cohort. Mean improvement in best-corrected visual acuity was 14.4 letters in the FYB201 group and 14.8 letters in the ranibizumab group.


**CATARACT**

**Outcomes After Cataract Surgery in Patients With DME**

**PATIENTS WITH DIABETIC MACULAR EDEMA (DME) WHO are actively managed with anti-VEGF injections before and after cataract surgery may experience mixed outcomes: While visual acuity (VA) may improve in these patients, their DME may worsen and perhaps require additional treatment, report researchers at the Mayo Clinic in Rochester, Minnesota.¹**

**Real-life outcomes.** For this study, the researchers retrospectively reviewed the charts of 30 patients (37 eyes) who underwent cataract surgery from Jan. 1, 2012, to Dec. 31, 2017. All were actively managed with anti-VEGF injections for DME before and after cataract surgery, with at least one injection within the six months preceding surgery. Most eyes (n = 22) received injections of bevacizumab.

**Visual acuity.** Before surgery, mean VA for all eyes was 20/107. This improved to 20/42 at post-op month 1 and to 20/35 at post-op month 6. However, at the six-month mark, the VA of three eyes was worse than it had been before surgery. In one of these three eyes, macular fluid also worsened following surgery.

**Retinal thickness.** While 30 eyes (81.1%) had fluid on the preoperative OCT, there were no statistically significant differences in central subfield thickness measurements before and after surgery.

**Worsening of DME.** “Perhaps the most surprising result was that 46% of eyes developed worse DME following cataract surgery,” said coauthor Sophie J. Bakri, MD. However, nearly all of these eyes did not have worse VA at any postoperative time point than did those eyes without new fluid.

**Active management required.** Careful patient selection may account for the surgery’s success, the researchers said.

“Our practice is conservative in choosing patients for cataract surgery, especially in those eyes with DME. The cataracts were visually significant, which is likely the reason patients saw a significant improvement in vision,” said lead author Matthew R. Starr, MD.

Dr. Starr added, “If a patient has a very dense cataract and can benefit from cataract surgery, the surgery is certainly warranted. However, patients need to understand they may need further intravitreal anti-VEGF injections and perhaps even more frequent follow-up” after surgery.

Dr. Bakri advised clinicians to actively control the DME preoperatively with intravitreal anti-VEGF injections. “Also, have a plan for postoperative management rather than an as-needed approach.” —Miriam Karmel


**HEADED TO MARKET?** If approved, biosimilars could lower the financial burden of AMD treatment.
visual acuity was 8.0 letters in both groups (7.8 ± 11.7 vs. 7.1 ± 10.42 letters for the FYB201 and ranibizumab recipients, respectively). The frequency and type of adverse events were comparable between the two groups, and most side effects were mild or moderate.

Given these results, Formycon announced in March that it will ask this year for approval of FYB201 as a biosimilar to ranibizumab in the United States and Europe. The company, based in Germany, said it is prepared for quick commercialization of the drug.

**Additional thoughts on biosimilars.** FYB201 is not the only potential biosimilar for AMD treatment on the regulatory horizon. A second possible biosimilar to ranibizumab, SB11 (Samsung Bioepis/Biogen), is under review at the FDA and the European Medicines Agency, based on positive outcomes reported last fall from a smaller, shorter-term clinical trial.

Although follow-up remains to be done to show FYB201’s longer-term safety, its approval as a biosimilar would have some potential advantages for ophthalmologists who treat AMD, Dr. Kaiser said. “Biosimilars in general have a much lower cost to obtain regulatory approval and as such are cheaper than the reference product. Moreover, approval in one indication garners approval for all the reference product’s indications, again lowering the cost.” (For more, see "Biosimilars in Ophthalmology," in the January 2021 Eyenet.)

Finally, how might FYB201 affect bevacizumab, the off-label alternative for treating retinal diseases? It won’t. “Bevacizumab is not a biosimilar,” Dr. Kaiser said. “It is a different medication with different binding coefficient, different molecular structure, and different efficacy in some indications, such as diabetic macular edema.” Moreover, he added, “there is a biosimilar of bevacizumab that is currently in phase 3 clinical testing for ophthalmic use.”

—Linda Roach

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**GLAUCOMA**

**Global Burden of Undetected Glaucoma**

**DESPITE DECADES OF PROGRESS** in glaucoma research as well as the advent of novel imaging technologies and surgical interventions, undetected glaucoma remains highly prevalent worldwide. There were an estimated 43 million cases of undetected primary open-angle glaucoma (POAG) in 2020—and this number is projected to rise to 67 million by 2040.

To look more deeply into these statistics, researchers in Singapore and Boston reviewed 61 articles from 55 population-based epidemiological studies published between Jan. 1, 1990, and June 1, 2020. The studies involved 189,359 participants; of these, 6,949 had manifest glaucoma, and 5,558 had undetected disease prior to diagnosis in the respective study.

**A global problem.** A meta-analysis of data by country of origin revealed that the average proportion of undetected cases in each geographical region varies significantly. Africa, for example, had the highest proportion (94%), whereas Oceania had the lowest (59%).

A second analysis, based on each country’s human development index (HDI), found that the proportion of previously undetected cases was above 90% in countries with a low HDI. That proportion fell to the 70% range in countries with medium to very high socioeconomic development.

The finding that 7 of 10 cases of glaucoma were undetected on average in developed countries was a surprise, said Ching-Yu Cheng, MD, PhD, at the Singapore Eye Research Institute. “Glaucoca detection is not just a problem in countries with low development.”

**Regional variations.** Africa and Asia had higher odds of undetected glaucoma, compared to Europe. (Differences between other regions and Europe were insignificant.) By 2040, the largest increase (86.3%) is projected for Africa, although Asia, by sheer population numbers, will account for 58.4% of all undetected POAG.

**Need for education.** “We ended our paper with a call to action,” said Dr. Cheng. He suggested a number of potential educational initiatives to improve glaucoma awareness and detection—and he encouraged clinicians to move ahead without waiting for formal initiatives. “Start advocating the importance of regular eye checks to the general public. And start checking for glaucoma in your next patient.”

—Miriam Karmel

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