EDITORIAL

Is This a 737 Max Moment for Brolucizumab?

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THE FIRST REPORTS OF SEVERE UVEITIS AND OCCLUSIVE retinal vasculitis associated with the use of brolucizumab (Beovu; Novartis, East Hanover, New Jersey, USA) appeared in early February of 2020, and more have appeared since then. Novartis sent information on the postapproval development to users on February 25 and updates have followed.[1] Twenty-six cases associated with 70,000 injections and 37,000 treated patients were reported by March 27, 2020, in a report by the American Society of Retina Specialists (ASRS) Research and Safety in Therapeutics (ReST) Committee.[2] Although the ASRS ReST committee report was not publicly available, the American Academy of Ophthalmology (AAO) has provided an available audio report on these recent developments surrounding brolucizumab-induced inflammation.[3] Neither the Novartis warning nor the latest ASRS ReST committee's report from April 7 recommended that brolucizumab injections be stopped, but they did recommend careful evaluation for inflammation and continued vigilance in monitoring brolucizumab treatment outcomes. However, for many of us, these recommendations did not go far enough, and we have stopped using brolucizumab because of the associated inflammation. Our patients have alternatives without incurring this risk.

When brolucizumab became commercially available in late 2019, the retinal community was enthusiastic about this newest vascular endothelial growth factor (VEGF) inhibitor for the treatment of exudative age-related macular degeneration (eAMD). Brolucizumab offered the hope of fewer intravitreal injections for patients with eAMD.[4] The brolucizumab phase 3 studies suggested greater durability with similar visual acuity outcomes compared with aflibercept (Eylea; Regeneron, Tarrytown, New York, USA). Who wouldn't want fewer injections into their eye and comparable visual acuity results? With good reason, both patients and clinicians embraced this new drug. However, soon after the widespread community adoption of brolucizumab, sporadic reports began to surface that patients were experiencing severe sterile inflammation that could be difficult to distinguish from infectious endophthalmitis. Although cases of severe sterile noninfectious intraocular inflammation have been reported following the injection of other anti-VEGF drugs,[5–11] this brolucizumab-associated inflammation was unusual because it was associated with an occlusive vasculitis and irreversible severe vision loss, albeit rare.[12–14] This unpredictable severe inflammation could develop weeks after the last brolucizumab injection even if previous injections of brolucizumab were well tolerated, so previous brolucizumab injections without inflammation were no guarantee that subsequent injections would be safe.[12–14]

The retinal community had not reported this type of vision-threatening occlusive retinal vasculitis after intravitreal injections of other commonly used anti-VEGF drugs, such as aflibercept, bevacizumab (Avastin; Genentech, South San Francisco, California, USA), and ranibizumab (Lucentis; Genentech). Retinal specialists started sharing this brolucizumab information with each other through social media, at meetings, and through published reports.[12–14] Unlike our previous experience with inflammatory outbreaks when using other anti-VEGF drugs, there had been no previous history of safe routine clinical use of brolucizumab before these reports of inflammation surfaced, so one of our initial impressions of this drug was one of heightened concern. Retina specialists deserve credit for identifying this problem early and notifying the appropriate authorities. They alerted Novartis, their specialty societies, and the Food and Drug Administration (FDA). As a result, both the ASRS and Novartis established committees to investigate this brolucizumab-induced inflammation. Novartis has willingly refunded the cost of any previously purchased brolucizumab to retina practices. However, brolucizumab remains on the market and continues to be used with the cautious approval of both the ASRS and Novartis.

Amid mounting speculation as to the underlying cause of this brolucizumab-associated inflammation, we all want the investigations to continue so we can learn the truth behind these adverse events. Whatever is learned from these ongoing investigations will provide invaluable information for anyone developing an agent for injection into the eye. But as this process plays out, it is our view that intravitreal injections of brolucizumab should stop. Brolucizumab is not the only drug that can be used for the treatment of eAMD.

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In the face of the known risk, its use is unwarranted. We praise the postmarketing surveillance of the vitreoretinal community in identifying these never-events, but now we need the ASRS, the Retina Society, the Macular Society, the AAO, and the FDA to make official what many retina specialists have already implemented—a moratorium on its use until the results of further investigations are concluded and remedies are implemented. Brolucizumab could fly again, but not until these safety concerns are addressed.

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