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An Update On Brolucizumab

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For our February 2020 Case of the Month, I presented a case of exudative macular degeneration treated successfully with the newest anti-VEGF medication to gain FDA approval for neovascular AMD, Beovu (brolucizumab). While the clinical trial data were strong for both efficacy and safety of this new medication, soon after the market release of Beovu, several cases of severe intraocular inflammation with associated retinal vasculitis were reported.

To review, Beovu was approved for the treatment of neovascular age related macular degeneration in late 2019. Clinical trials demonstrated non-inferiority in terms of visual acuity gains at 48 weeks compared to Eylea, and over 50% of patients on Beovu were able to be kept dry on an every 12 week dosing schedule. Beovu was the first anti-VEGF agent to be approved for Q12 week dosing.

In late February 2020, however, the American Society of Retina Specialist published a safety update which described 14 cases of severe intraocular inflammation following Beovu injection, the majority of which also had occlusive vasculitis. While there is a known risk of intraocular inflammation following intravitreal injection with all agents, generally these events do not result in permanent visual loss. The vasculitis component reported following Beovu injection was different than what had been seen with other agents, and many patients experienced significant and permanent vision loss. This rightfully alarmed retinal specialists. Other reports soon surfaced, and Novartis convened a group of experts to study the findings

Since the first reports in February, we have learned additional information about the clinical presentation, and frequency of this adverse event. Unlike acute, infectious endophthalmitis, which typically presents within 1 week of intravitreal injection, Beovu associated inflammation presents later, often over 30 days following injection. Early data are limited, but women seem to be affected more frequently than men. Patients most often complain of floaters, and reduced vision. Pain is a less common complaint. All patients have vitritis, and most have anterior chamber inflammation. Perhaps the most worrisome sign is vasculitis, which may be occlusive. The vascular inflammation may affect both large and small vessels, and can involve the optic nerve, posterior pole, periphery or be multifocal. Arteries tend to be first affected, followed later by veins. Unfortunately, the occlusive vasculitis can lead to permanent and severe vision loss, in some cases to the level of counting fingers or worse.

The cause of inflammation remains uncertain. Because of the delay in onset, and the fact that many affected patients received multiple injections prior to developing the reaction, it is postulated to be a delayed hypersensitivity reaction rather than a direct toxic effect. Whether this is secondary to the drug itself, or some impurity from the manufacturing process remains unclear. Novartis and the retina community as a whole continue to investigate.

One of the most important pieces of information necessary to determine whether Beovu use is worth the risk, is the frequency that severe inflammation, vasculitis and vision loss occurs. As of September 2020, the post-

marketing data put the incidence of retinal vasculitis alone, retinal vascular occlusion alone, or the combination of both at 13.64 per 10,000 – or more than a 1 in 1000 chance per injection. The incidence of vision loss associated with these events was 4.86 per 10,000. These data likely under-report the true incidence of events because it relies upon voluntary reporting from the community, and does not occur in a controlled clinical trial environment. Perhaps the best data that we have come from a post-hoc analysis of the Hawk and Harrier trials which was conducted by an unmasked safety committee convened by Novartis. After review of all data, 50 out of 1088 (4.6%) study eyes were identified that developed inflammation following Beovu injection. 36 of these (3.3% of 1088) developed vasculitis and 23 (2.1% of 1088) developed vascular occlusions. Despite the high rate of this reaction, no statistical difference was found between the rate of ≥15 letter visual acuity loss in the Beovu and aflibercept groups (7.4% vs. 7.7%). Although this reassured the FDA enough to keep the drug on the market, many retina specialists, including our group, believe that odds of 1 in 50 that an injection could result in vascular occlusion is unacceptable – especially when some of these patients will end up with severely and permanently reduced visual acuity, and/or scotoma. Given that other safe and effective therapies exist for neovascular AMD, and that we currently have no way of predicting who will be affected by occlusive vasculitis, we have elected to avoid Beovu until safety can be demonstrated.

We advise that all ophthalmologists and optometrists maintain a high degree of suspicion in patients presenting with floaters, decreased vision or pain following Beovu injection. We will continue to update our referring community regarding any new updates.

Take Home Points

- Brolucizumab (Beovu) is the newest anti-VEGF agent to be approved for exudative macular degeneration
- A unique inflammatory response consisting of vitritis, vasculitis and vascular occlusion has now been described following Beovu injection with a frequency which may be as high as 1/50 injections.
- Patients affected by this response may suffer irreversible vision loss.
- Because alternative, effective and safe medications exist, our group has decided to hold further Beovu injections until more is understood about this adverse reaction.

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