Beovu: What's the latest with the ophthalmic community's concerns?

by Sam McCommon

Reports and opinions keep pouring in about Novartis' Beovu® (brolucizumab), meant to treat wet or neovascular age-related macular degeneration (nAMD). In February, the American Society of Retina Specialists (ASRS) noted a risk of intraocular inflammation and retinal vasculitis associated with the drug; more concerning was that 11 of the 14 cases of vasculitis were occlusive retinal vasculitis, which can lead to vision loss. The drug's main appeal is that it reduces the rate of injection to once a quarter following the initiation of treatment.

Novartis backed these findings in April, noting a "confirmed safety signal of rare adverse events of retinal vasculitis and/or retinal vascular occlusion that may result in severe vision loss." Novartis' safety review committee (SRC) noted a 3.3% rate of retinal vasculitis in study patients who had been treated with Beovu. Most of the patients (74%) experienced symptoms within six months of the treatment, though some (12%) experienced it as late as 12-18 months afterwards. According to an ASRS report, the earlier events were associated more frequently with moderate or severe vision loss.

Fast forward to May, and an editorial in the *American Journal of Ophthalmology* asked if this was a 737 MAX moment for brolucizumab, drawing a connection between the drug and Boeing's flawed flyer. Authors Philip J. Rosenfeld and David J. Browning asserted that, as there are other drugs currently available to treat wet AMD, there is no reason to subject patients to the risks associated with Beovu. They argued that previous warnings hadn't gone far enough: While announcements from the ASRS and Novartis did note the risks associated with the drug, they didn't call for stopping its use. These authors took that stop and called for its halt.

"In the face of the known risk, its use is unwarranted," they wrote. "We praise the post-marketing 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."

Other drugs currently on the market have not been associated with the same levels of intraocular inflammation (IOI). As the authors said, "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 (Eylea; Bayer, Leverkusen, Germany), bevacizumab (Avastin; Genentech, California, USA), and ranibizumab (Lucentis; Genentech, California, USA). Retinal specialists

started sharing this brolucizumab information with each other through social media, at meetings and through published reports."

So the new kid on the block has raised a few eyebrows. Where are we now? To get a clearer view of the picture, we reached out to Dr. Kenneth Fong, president of the Malaysian Society of Ophthalmology.

Doctor's orders

Dr. Fong acknowledged the concerns brought up by the ASRS and confirmed by the SRC. "These reports of retinal vasculitis in patients receiving brolucizumab are very concerning as such side effects have not been observed in millions of patients treated with the current choices of anti-VEGF agents: bevacizumab, ranibizumab or aflibercept," he said.

"Patients receiving brolucizumab should be informed of this potentially serious side effect before treatment," he added. Doctors who administer the drug should be aware of the current findings, and pass the information along to their patients.

Dr. Fong noted that he has only used Beovu for a small number of patients as part of a study that compares the drug to aflibercept for diabetic macular edema (DME).

Is it any use at all?

Despite the calls for the drug's use to be halted by the authors of the AJO op-ed, there may still be some use for Beovu. However, it may not be the go-to, frontline drug for nAMD that Novartis had previously planned.

"In my practice, brolucizumab is a potential second line agent for patients that have not responded to the current line of anti-VEGF agents available, which all have excellent long-term visual acuity gain and safety profiles," said Dr. Fong. "Despite the fact that it is FDA approved for wet AMD, it would be hard to recommend it as a first line agent until the safety issues have been clarified further."

Dr. Fong further pointed out that the risk of serious vision loss — a loss of more than 15 letters — was at 0.7% according to the current studies. So, while upwards of 99 out of 100 patients do not suffer severe vision loss, the risk is still there. Nobody wants to be that one in 100.

To Novartis' credit, they've received praise from the ophthalmic community for their transparency and quick action regarding the drug. Once the risks are better understood, the drug could come roaring back and be that frontline player it was meant to be. The company defended the drug's value as a treatment and reaffirmed their commitment to transparency.

As a company spokesman said, "Novartis believes that Beovu continues to represent an important treatment option for patients with wet AMD, with an overall favorable benefit-risk profile. We are committed to collaborating with the scientific community to better understand the causes, potential risk factors and management of these events."

What's next for Beovu?

The drug is being investigated, as the reason behind its link to IOI is still unknown. The drug is still on the market, and its use will have to be decided at each doctor's discretion. As the ASRS's ReST committee noted, "With all therapeutics, the risk of adverse events and their visual consequences need to be balanced with potential benefits. The ReST Committee believes that this risk-benefit assessment at the individual patient level is best determined by the judgment of the treating provider."

As to the cause? We don't yet know, but Dr. Fong has a theory.

"The reason for retinal vasculitis is unclear," he said, "but it is probably an immune mediated reaction to the drug and that is the possible reason for delayed appearance of this side effect after 6 months."

One interesting note the ReST committee pointed to is that brolucizumab and aflibercept share roughly the same risk of vision loss over time: 7.4% and 7.7%, respectively. The ASRS report does not indicate what causes said vision loss; just that it occurs.

Novartis stock took a significant hit in February and into March, though the drop was concurrent with wider market trends. It has since clawed back around half of its losses and share prices have been essentially steady between April and June, as of this writing.

With millions of patients being treated for wet AMD, doctors will need to take note of any updated information regarding Beovu. Retinal vasculitis has not been reported as a result of the other current, popular drugs, so their use will likely continue. Patients who were hoping for a reduced injection regimen may have to put up with the current rate of injections — unless they and their doctor decide going off the reservation is worth the risk.

Contributing Doctor

Consultant Vitreoretinal Surgeon **Dr. Kenneth Fong**, MA MB BChir (Cambridge), FRCOphth (UK), FRANZCO (Aust), CCT (UK), AM (Mal), is recognized as an ophthalmologist in the UK, Australia and Malaysia. He graduated with a medical degree from the University of Cambridge in 1998 and trained to be an eye surgeon in London. Dr. Fong then spent two more years training in the UK and at the Royal Perth Hospital in Australia to subspecialize in retina. After 18 years of working in the UK and Australia, he returned to Malaysia in 2009 to serve as associate professor and consultant ophthalmologist and retinal surgeon at the University of Malaya in Kuala Lumpur. He is currently the managing director of OasisEye Specialists in Kuala Lumpur. Dr. Fong is the president of the Malaysian Society of Ophthalmology and serves as a council member for the Asia Pacific Vitreo-retinal Society.

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