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COMMENT

Brolucizumab-related retinal vasculitis: emerging disconnect between clinical trials and real world

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Brolucizumab is the most recently approved anti-vascular endothelial growth factor (anti-VEGF) agent for neovascular age-related macular degeneration (nAMD). Abicipar pegol is another agent that has been filed for marketing approval with the United States Food and Drug Administration and the European Medicines Agency [1, 2]. The common aspect of these molecules is the low molecular weight, a different structure compared to the previous anti-VEGF molecules, and the occurrence of an emerging phenomenon of retinal vasculitis in the phase 3 trials. [3, 4].

The arrival of brolucizumab was highly anticipated by the ophthalmological community due to its better fluid control despite its less frequent recommended dosing schedule in eyes with nAMD. It also provided a new option for eyes that were non-responsive to the previously available anti-VEGF options such as ranibizumab (Lucentis, Novartis) and aflibercept (Eylea, Bayer). Seventy thousand doses of the molecule have been administered till April 1, 2020. [5]. The brolucizumab early real-world study (BREW), an early real-world visual outcome report has been recently published by our group [6]. Forty-two eyes of 42 patients, previously treated with other anti-VEGFs that underwent 60 injections of brolucizumab showed significant improvement in the mean central sub-foveal thickness, while maintaining the best-corrected visual acuity. Our study did not find any safety flag during the follow-up period.

But safety concerns have been raised due to the incidence of intraocular inflammation (IOI) in eyes receiving brolucizumab, most severe of which is the occurrence of visual loss in 30% of the patients developing retinal vasculitis and/or retinal vascular occlusion [7]. Due to the predefined criteria for reporting adverse events (AE), the cases with the combined occurrence of retinal vasculitis with retinal vascular occlusion are not being termed as retinal occlusive vasculitis. Such combined incidences have now been reported to be occurring at a rate of 4.6 per 10,000 injections in the post-marketing surveillance, as reported on 26th June 2020 [7]. The HAWK and HARRIER trials safety audit has revealed an overall 2.1% incidence of retinal vascular occlusion with retinal vasculitis. The difference in the incidence might be because of treatment naive eyes that were recruited in the phase 3 trials. New safety signals have not been reported earlier with other anti-VEGFs that have graduated from clinical trials to the real-world. Brolucizumab though, in contrast, was reported to cause retinal vasculitis in the real-world data, which was also found to be present in the clinical trials data set on the additional safety review. This curious phenomenon raises the possibility of a difference in the incidence rate among treatment-naive and previously treated patients of nAMD. The MERLIN trial, which has recruited 530 patients with persistent retinal fluid despite being treated previously with other anti-VEGF agents may provide us with a better data set that will more closely resemble the real-world target population [8].

The published literature on these AE gives us some insight into the clinical presentations. The IOI preceded the vasculitis phenomenon, which had an arterial preponderance. All cases in the published reports were female patients, who had already been treated with multiple anti-VEGF injections before being switched to brolucizumab,

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which is in stark contrast with the treatment-naive cohorts in the phase 3 trials [3, 9–11]. The alert issued by the American Society of Retina Specialists reports 88% of the 26 eyes of 25 patients were females [12]. The published cases have also revealed that 8 of the 14 patients had some form of systemic auto-immune conditions while three patients had a history of breast cancer. However, a systemic association looks less likely due to the absence of bilateral involvement in eyes with unilateral injection, as well as the higher mean age group of the population which does not favour an auto-immune component. The data set at the current point of time is too small to prove a causative association either with gender or systemic conditions, but such a relationship, especially a gender preponderance should be studied in further trials and real-world analyses.

IOI has been reported previously with other anti-VEGF agents, the causative factor being the fractionation technique, counterfeit medications of bevacizumab [13], high endotoxin levels in razumab (Intas, India) [14], (the biosimilar to ranibizumab) or the faulty kit with aflibercept [15]. The vasculitis though has only been noted in abicipar pegol's phase 3 trial CEDAR and SEQUOIA [4]. The detailed nature of these AE in the context of their association with inflammation or retinal vascular occlusion has not yet been published. The incidence of vasculitis reduced to nil with an improved manufacturing process as reported in the MAPLE trial, and thus the probable causative agent was the E. coli fragments rather than the smaller molecular size [16].

The smaller molecular size of brolucizumab which is a single-chain variable fragment (scFv) with absent Fc portion allows for a high molar concentration to be injected into the intra-vitreal cavity [17]. The type III hypersensitivity reaction, which has been implicated in retinal vasculitis caused by deposition of the antigen-antibody immune complex has been highlighted by our group previously. The high antigenic load due to the increased molar concentration is coupled with a high rate of anti-drug antibodies (ADA) in the population. Though the pre-existing ADA (36–52%) in the treatment naive eyes of the HAWK and HARRIER trials were the highest ever to be reported among all the anti-VEGF agents, it is postulated to be due to the small size of the molecule and probable resemblance with systemic non-specific small proteins rather than the antigenic nature of the molecule [18, 19]. The treatment-emergent ADA, which forms a better indicator of the antigenicity, has been noted in association with the incidences of IOI [7]. These antibodies are specific to brolucizumab and thus have more propensity of developing immune complexes when present in the correct stoichiometric ratio lead to tissue deposits, inflammation and damage, features consistent with retinal vasculitis.

There are multiple ongoing trials involving brolucizumab in conditions such as nAMD with persistent retinal fluid, diabetic macular oedema (DME) and retinal vein occlusions (RVOs). The worst-case scenario of eyes developing retinal vasculitis with retinal vascular occlusion has been postulated to be between 0.8 and 2.9% in these trials [7]. The association of treatment-emergent ADA to ranibizumab and inflammation has been noted in eyes with nAMD and not in eyes with DME and RVOs [20]. These future trials thus hold a key to the understanding of the role of ADA in the development of vasculitis.

Brolucizumab has to date been approved for use in more than 40 countries including USA, EU, Japan, Australia, Argentina, Switzerland, and India. Ophthalmologists have also started to use the drug in indications other than nAMD, such as advanced Coat's disease [21]. With the recent incidences of AE, the drug is bound to be closely scrutinised. The gender preponderance, the status of treatment-emergent ADA, and the association with the disease process are the few parameters that should be analysed in the real-world to understand the pathophysiology of the incidence of retinal vasculitis with retinal vascular occlusion.

Compliance with ethical standards

Conflict of interest AS: Consultant: for Novartis, Allergan, Bayer and Intas. FB: Consultant: Allergan, Bayer, Boehringer- Ingelheim, Fidia Sooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. BDK: Clinical research: Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, ThromboGenics; Consultant: Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, Theravance Biopharma. AL reports other from Allergan, other from Novartis, other from Roche, other from Notal Vision, other from Forsights labs, other from Beyeonics, other from Bayer Health Care. NK: None. NP: None. SS: None.

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