

Current perspectives on use of anti-vascular endothelial growth factor agents for retinal disorders

The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has led to paradigm shifts in management of retinal disorders of various etiologies. We have come a long way from macular photocoagulation for neovascular age-related macular degeneration (nAMD) and grid laser photocoagulation for macular edema secondary to vein occlusions (RVO) and diabetic retinopathy (DME). The fact that intravitreal injections have become mainstay in the treatment of these diseases is common knowledge now and most ophthalmologists do not hesitate in initiating treatment. Yet there appears hesitancy in advising reinjections. In this editorial, I discuss important aspects of treatment regimens and various different drugs available to us, with special emphasis on biosimilars and newer agents that have the potential to revolutionize treatments and reduce treatment burden.

When it comes to treatment regimes, the choices stem from various arms of different clinical trials in the past. A loading dose, that is, one injection every month for the first 3 months is recommended for most pathologies. Following this, we can opt to continue *monthly injections* or inject as and when required (*pro re nata i.e., PRN*) provided patients maintain monthly follow-ups. However, it has emerged from some of the pivotal clinical trials that a purely PRN regimen possibly leads to suboptimal outcomes, especially in nAMD.^[1] A *treat and extend regimen (T&E)* is an intermediate option between continued monthly and PRN regimens where, after a loading dose, monthly injections are continued till disease activity ceases and then intervals for the next injections are extended by 2 additional weeks every time from the previous injection, up till a maximum of 12 weeks, irrespective of disease activity. Some recent surveys of retina specialists have shown that this is the most preferred regimen used by most to reduce treatment burden yet maintain benefits of treatment.^[2] In patients who do well, have stable vision and do not show persistent disease activity, another possible regimen is *observe and extend* where interval between subsequent visits are extended by two additional weeks from the previous visit without reinjecting at each visit. A lot of the times, patients drop out of one particular regimen and merge into lesser stringent regimens either due to financial constraints or lack of perceived benefits with existent regimens. Given all these options, the T&E is possibly the best way forwards in current times. Once ophthalmologists believe in this, it is vitally important to convey the different regimes to patients and get them to trust in the need for repeated injections. Hesitancy in this discussion right at the beginning can lead to a lot of mistrust and poor outcomes. Though there is no large-scale survey amongst general ophthalmologists in India about which regimen they prefer, I suspect that many may not be convinced about benefits of a loading dose or relentless reinjections despite persistent disease activity. Without conviction of self, it is difficult to convince patients of these benefits. It is my endeavor to persuade general ophthalmologists to have a low threshold for repeat injections and adopt a T&E regimen whenever possible and financially feasible for patients.

Ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA) was the first FDA-approved anti-VEGF to become available for nAMD and was subsequently cleared for use in other conditions. Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc, Tarrytown, New

York, and Bayer HealthCare, Berlin Germany) is the other FDA approved anti-VEGF and has shown very similar or slightly better results when compared to ranibizumab, albeit only for certain subgroups and better results were not sustained over longer follow-up.^[3] In the majority of the developing world where insurance coverage for intravitreal injections is lacking and patients are paying out of pocket, affordability becomes the major hindrance in view of the high treatment burden. Despite differential pricing making ranibizumab significantly cheaper in India (Accentrix, Novartis India Ltd, Mumbai, India) compared to the developed world, our patients still find it difficult to afford repeated injections. Cheaper options include use of intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA and Roche, Basel, Switzerland) in an off-label fashion, with the major drawback being a higher risk of endophthalmitis, as evidenced by a recent outbreak in India due to use of counterfeit vials.^[4] Additionally, a more detailed look at clinical trials comparing bevacizumab with ranibizumab shows that outcomes, both anatomical and functional, are not as good with the former, especially when used PRN.^[1] Another potentially cheaper alternative is Ziv-aflibercept (Zaltrap, Zaltrap; Regeneron, Tarrytown, NY and Bayer Healthcare, Leverkusen, Germany), a systemic analog of aflibercept, where one vial can be used to inject several patients, thereby reducing costs. Several studies have shown a good efficacy of this drug but again,^[5] risk of infection, off-label nature of use and difficulty in procurement have limited its use.

In view of the heightened demand of intravitreal anti-VEGF's on one hand and prohibitively high cost of innovator molecules and high treatment burden on the other lead to a huge void for retina physicians and their patients wanting good outcomes. This void has been addressed by the availability of biosimilar ranibizumab (Razumab, Intas Pharmaceuticals, Ahmedabad, India) that is significantly cheaper than its innovator cousin, and limited papers have shown it to have good efficacy in all major retinal pathologies.^[6] In this issue of the IJO, Verma *et al.* present results from the retrospective CESAR study and show excellent results in nAMD ($n = 70$ eyes), DME ($n = 70$ eyes) and RVO ($n = 13$ eyes).^[7] Similarly, results from the vitreoretina society of India (VRSI) survey on biosimilars, also published in this issue of the IJO,^[8] clearly shows increasing acceptance of the ranibizumab biosimilar by retina physicians in India with over 100,000 injections used up to 2020. Though these data and individual experiences show the drug to have good efficacy, a comparative study with the innovator ranibizumab is still lacking making purists still adhere strongly to the innovator molecule wherever financially feasible. Given the extremely high demand, several other companies are also trying to manufacture ranibizumab biosimilars. A bevacizumab biosimilar is also available in India (Zybev, Zydus Cadila, Ahmedabad, India), though fewer than 25% retina specialists prefer to use it for obvious reasons.

Lastly, need for repeated injections, increasing incidence of retinal diseases and affordability issues associated with repeat injections has driven us to look for potentially longer acting formulations with equal or better efficacy. Brolicizumab (Beovu, Novartis Pharma AG, Basel, Switzerland), recently launched in India (as Pagenax, Novartis India Ltd, Mumbai, India) appears to tick all these boxes in having a longer duration of action (about 3 months) and excellent efficacy results for nAMD in comparison to aflibercept from recently conducted multicentric randomized clinical trials.^[9] However, just when retina physicians and patients were enthusiastically looking to embrace this new drug, anecdotal reports of retinal toxicity started emerging. More recently, two relatively large series have documented intraocular inflammation with this drug, with some cases having experienced occlusive retinal vasculitis with

irreversible vision loss.^[10,11] Though intraocular inflammation has been reported in its initial period with both ranibizumab and aflibercept, brolucizumab is the only FDA approved anti-VEGF that has resulted in retinal vasculitis thus far. In this issue of the *IJO*, Narayanan *et al.* report a case of sterile endophthalmitis that occurred within the first 24 hours after injecting brolucizumab.^[12] Though the eye recovered with intensive steroids alone, this is never the less a disturbing adverse event that we need to watch out for. Lets hope that the incidence of inflammation will reduce over time as the manufacturing process of brolucizumab becomes more robust and that the drug will be able to realize its full potential as a potent anti-VEGF that reduces frequency of injections without losing efficacy.

In conclusion, choice of anti-VEGF depends upon patient affordability more than science. However, almost every patient will require repeated injections to get optimum outcomes, with treat and extend the most favored regimen at present. Every ophthalmologist should discuss this with his/her patient before starting therapy. Potent longer acting drugs are now available to us that promise even better outcomes with fewer injections, though judicious adoption and high index of suspicion for drug-induced inflammation are needed till the incidence of such events reduce.

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