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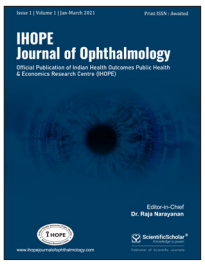

Guest Editorial

Intravitreal anti-VEGF agents – The way forward

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The advent of antivascular endothelial growth factor injections over the past 15 years has revolutionized the management of retinal vascular diseases including macular neovascularization (MNV), retinal vein occlusions (RVO), diabetic macular edema (DME), and many other disorders that fall under the gamut of vasculopathies. This field of research has constantly evolved with newer drugs and newer treatment regimens such that we are now at the doorsteps for individualized treatments for patients depending on the disease activity. In this manuscript, I discuss how treatment regimens have evolved overtime, different agents available to us, and efforts to improve patient compliance, especially in the Indian scenario.

The pivotal ANCHOR and MARINA trials showed excellent results in MNV but the recommended treatment regimens of monthly injections for long periods of time,[1] irrespective of disease activity, levied a tremendous economic burden on the health-care system, and it soon became apparent that this was untenable. PIER[2] and other studies looked at lower frequency fixed dosing schedules but could not match the visual gains of the ANCHOR and MARINA. In view of this, the PronTo study[3] recommended a 3 monthly loading dose followed by variable dosing schedule based on an as needed basis (*pro re nata,* i.e. PRN) and gave reinjection criteria based on visual acuity, optical coherence tomography findings of fluid, and clinical signs of reactivation such as new subretinal hemorrhage. Yet, visual results did not closely match the pivotal trials and monthly follow-ups were still recommended. To overcome the problem of visual under performance with injections and balancing adequate follow-up intervals, and given that it is now apparent that MNV almost always reoccurs if left untreated for a period of time, the treat and extend (T and E) protocol is the most preferred now. In this, after a loading dose, monthly injections are continued till disease activity seizes 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. This approach has been validated by several large multicentric clinical trials and is possibly the best way forwards till be find a more robust regimen that addresses individual needs of patients.[4] The T and E regimen has percolated into management of RVO and DME as well where, after an initial loading of minimum three injections and then achieving a dry retina, we look to increase the interval between injections gradually to maintain the visual benefit gained from the initial flurry of injections.

In terms of the drugs available, we have seen exciting developments after ranibizumab was introduced and the pace has recently picked up with many new and exciting agents available or in the pipeline and hitting clinical trials soon. Aflibercept was the first one to be introduced as an alternative to ranibizumab and showed excellent results in most comparative trials, though the non-inferiority study design of most trials does not allow assessment on

superiority in different aspects of disease including vision and macular status. Other alternatives include use of biosimilars of ranibizumab and off-label bevacizumab and ziv-aflibercept. There are lot of doubts and apprehension among the retina specialists regarding legal implications of the use of intravitreal bevacizumab or its biosimilar due to its off-label use in ophthalmology and not approved by the Food and Drug Administration, USA, nor by the Drug Controller General of India. However, there are numerous trials performed worldwide assessing the safety and efficacy of intravitreal bevacizumab when compared to other anti-VEGF. In the Indian context, this is important as it has an added advantage of decreasing the economic burden of treatment by significantly reducing the cost of therapy. Furthermore, to prevent the use of spurious or counterfeit bevacizumab, the expert committee has agreed to introduce a Kezzler code which is a unique alpha-numeric code printed on each vial of the drug. The validity and genuineness of the drug can be confirmed from the manufacturer directly by messaging the code using the short message service. Over the past 2 years, newer agents such as brolucizumab, abicipar pegol, and faricimab, all of which promise greater durability translating into lower injection frequency, have all been into clinical trials. Of these, brolucizumab has reached clinics globally and real world experience shows excellent efficacy results. However, both brolucizumab and abicipar have faced issues of intraocular inflammation (IOI),[5,6] including occlusive retinal vasculitis, at an incidence that is above acceptable limits. There is a lot of research going into the exact pathogenesis of these IOIs, thereby dampening the initial euphoria and expectations. The ophthalmic scientific community still awaits answers from the innovators to resolve this puzzle, but I am positive that we will get over this. In my opinion, there is possibly a tipping point into how much VEGF we can inhibit and once that is crossed, as with brolucizumab or other molecules, there are likely to be adverse reactions. Other factors such as racial differences in incidence of IOI that have emerged with real-world experience (e.g., IOIs appear to be less frequent in India) also need to be explored soon. A good way to maintain benefit with these drugs is to use them as intended, that is, at lesser frequency of every 3 months or so, and not push boundaries and inject more frequently.

Finally, in an ideal scenario, we would like to use the most effective treatment for each patient ignoring the cost of the medicine; however, in the real world, the scenario is the opposite. These therapies are cost prohibitive for most of the developing world leading to poor compliance and more than half patients not following through even with T and E regimen. Recently, the Government of India has approved reimbursement for intravitreal injections under most insurance plans and the mandate for implementing this is with the Insurance Regulatory and Development Authority (IRDAI) of India. It has been more than 6 months since this is applicable and we are now seeing many patients getting reimbursed which should eventually improve compliance. Questions still remain about the total annual sum available for reimbursement, number of injections covered, and types of injections covered.[7] There needs to be better dialogue between the IRDAI, insurance providers, physicians, patients, and pharmaceutical companies to ensure smoother and more equitable implementation of these newer regulations. In addition to insurance, the injection providers are also providing patient assistance programs including few subsidized injections as well as education and need for sustained treatment throughout the process. Cost-effectiveness is only one consideration in choosing a treatment. We are hopeful that in future with various measures undertaken by the government agencies and insurance companies we would choose a particular drug depending on the needs of particular patients, which can vary depending on their economic circumstances, their support networks, the treatments they have previously tried, their lifestyles, and their overall health. We are hopeful that these initiatives will bear fruition and more patients will receive the much needed anti-VEGF injections at more affordable costs.

In conclusion, we are in a new era in terms of management of retinal vascular diseases. Although effective, more work is required to individualize treatment regimens with anti-VEGF injections using emerging technology such as home-based OCT monitoring. Newer drugs with longer duration of action and better safety profiles are required at affordable costs to help majority patients maintain vision over the next decade.

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