Commentary: Ziv-aflibercept: An alternative antivascular endothelial growth factor agent for polypoidal choroidal vasculopathy

The glory of medicine is that it is constantly moving forward, and there is always more to learn. Our understanding of polypoidal choroidal vasculopathy (PCV) has come a long way since the time it was first described by Dr. Yanuzzi in 1982, as polypoidal, subretinal, and vascular lesions associated with serous and hemorrhagic detachments of the retinal pigment epithelium.[1] Our understanding of the pathophysiology of PCV has improved due to the advancements in indocyanine green angiography and optical coherence tomography angiography. The lesions are now considered to be part of the pachychoroid spectrum with development of the neovascular component.[1] Subsequently, the treatment methods have also evolved with our understanding of pathophysiology.

The EVEREST II clinical trial demonstrated that verteporfin photodynamic therapy (PDT), alone or in combination with ranibizumab, was superior to ranibizumab monotherapy in improving visual acuity and achieving complete polyp regression at 12 months.[2] However, concerns with the side effects such as choroidal ischemia and late retinal atrophy eventually leading to visual loss have resulted in PDT being used as a rescue therapy while the mainstay of the treatment is anti-vascular endothelial growth factor (VEGF) monotherapy. Several reports have evaluated ranibizumab as well as the off-label bevacizumab for treatment of PCV.[3] Favorable results were seen with anti VEGF monotherapy with comparable visual outcomes.[3] Although ranibizumab was shown to be more effective in regressing polyps, there was a lot of variation in the treatment response of PCV; small-sized PCV responded well to anti-VEGF therapy and/or PDT but lesions with choroidal hyperpermeability or pachychoroid showed poor results.[4] PDT is usually reserved for recurrent lesions or patients whose follow up will be difficult.

Aflibercept (Eylea, Bayer, Leverkuensen, Germany), another anti-VEGF agent which inhibits VEGFA, VEGFB, and placental growth factor, has rapidly gained ground in the treatment of neovascular age-related macular degeneration (AMD). Several trials that reported similar efficacy, lower frequency, and improvement in patients with poor response to ranibizumab and bevacizumab have rapidly made aflibercept an alternative, if not a first-line therapy for AMD. When used in the treatment of PCV, it was seen to be more effective than ranibizumab in causing polyp regression as well as visual improvement.[5]Subsequently, PLANET study demonstrated the superior efficacy of intravitreal aflibercept monotherapy over PDT rescue therapy.[6] It confirmed improved visual and functional outcomes in more than 85% of patients and the authors did not find a reason to recommend PDT. It was also reported that for PCV patients who are refractory to ranibizumab, switching to aflibercept is generally effective.[5]Although aflibercept continues to dominate as the anti-VEGF of choice, its affordability is a big hurdle for the drug.

As with any disease condition, the ultimate goal of PCV treatment is to achieve best possible visual outcome while minimizing the financial burden. Ziv-aflibercept (Zaltrap, Sanofi, Paris, France), a systemic antiVEGF agent approved for the treatment of metastatic colon cancer has been recently tried in place of aflibercept. A 2-year study by Chan *et al*. reported that intravitreal injection of ziv-aflibercept was found to be effective against macular edema secondary to diabetes and retinal vein occlusion as well as AMD.[7] They have also reported improvement in BCVA and central macular thickness (CMT) with few side effects. Moreover, Chan *et al*. have reported that the outcomes of ziv-aflibercept in treating PCV were comparable to the outcomes of other major studies involving aflibercept, in terms of improved visual acuity and polyp regression.[7] Singh *et al*. also have reported better outcomes in treating PCV using ziv-aflibercept with improvements in visual acuity and reduction of pigment epithelial detachment as compared to using bevacizumab.[8] The authors noted no untoward effects of the ziv-aflibercept and thus concluded that it was a safe option for the treatment of PCV.

However, it would be prudent to note that ziv-aflibercept has a higher osmolarity of 815–829 mOsm as compared to 250–260 mOsm osmolarity of aflibercept. A study by Marmor *et al*. has reported that intravitreal injection of 0.05 ml of a solution with osmolarity >500 mOsm can result in retinal toxicity, including retinal detachment.[9] So far, the studies have not reported any retinal toxicity with ziv-aflibercept.

Nevertheless, these off-label, less expensive, alternative anti-VEGF agents certainly help reduce the treatment costs to a fraction of those of the approved agents. This might prove to be more cost effective and beneficial, especially in the developing world where majority of the patients cannot afford these drugs. However, the studies conducted so far are of small scale with limited follow up. Better-designed, large population studies with a long follow-up period will help us understand the true potential implications of these alternative agents.

Kumar Anshuman, Dhanashree Ratra

Department of Vitreoretinal Diseases, Medical Research Foundation, Sankara Nethralaya, 41/18, College Road, Chennai, Tamil Nadu, India

Correspondence to: Dr. Dhanashree Ratra, Department of Vitreoretinal Diseases, Medical Research Foundation, Sankara Nethralaya, 41/18, College Road, Chennai - 600 006, Tamil Nadu, India.
E-mail: dhanashreeratra@gmail.com

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