Commentary: Switching of anti-vascular endothelial growth factor agents in refractory diabetic macular edema

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) are widely accepted as the current gold standard for the treatment of center involving diabetic macular edema (DME). The efficacy of these injections has been proven in many large randomized controlled trials. However, a percentage of patients in these trials showed poor response to the anti-VEGF agent. Approximately 50% of cases treated with bevacizumab in the Protocol T study did not respond and had persistent macular edema at 2 years.[1] In the Protocol I study, among the patients treated with ranibizumab, 52% failed to achieve ≥2 line vision improvement, and 40% had persistent edema.[2] However, the definition of a non-responder is not quite certain. The patient is labeled as non-responder if there is less than 5 letter visual gain or less than 10% decrease in the central retinal thickness after a minimum of 3 injections over 12 weeks time period.[3]

Some patients might not respond to anti-VEGF from the beginning itself but more often, the non-response is seen after an initial good response. The reason for non-response is unclear but tachyphylaxis is thought to be responsible. Tachyphylaxis is the diminished therapeutic response to a drug after it has been administered repeatedly. Prolonged treatment for exudative age-related macular degeneration has been shown to result in tachyphylaxis for both intravitreal bevacizumab as well as ranibizumab.[4] The reason for the tachyphylaxis phenomenon has been speculated to be due to immune response to the anti-VEGF antibodies. Circulating neutralizing antibodies develop against these humanized biologics which cause rapid clearance of the anti-VEGF antibodies from the system. Such antibodies are more common after systemic administration of biologics such as infliximab. But smaller amounts of circulating neutralizing antibodies have been demonstrated against ranibizumab as well as bevacizumab.[5] The upregulation of VEGF receptors is also another theory proposed to explain the phenomenon of tachyphylaxis. Apart from this, the non-response may also be due to disease reactivation or increased VEGF expression from the inflammatory cells.

The problem of non-response is addressed by switching the therapeutic agent. Generally, a switch to another pharmaceutical class such as corticosteroids is considered. Dexamethasone implant has a broad antiangiogenic as well as anti-inflammatory action. It is shown to be more effective in drying the retina and has proven its efficacy in chronic, non-responsive diabetic maculae edema.[6] However, a switch to another anti-VEGF agent is also possible. Several small studies have shown the benefit of switching to ranibizumab in DME patients who are non-responsive to bevacizumab.[3]

Switching to aflibercept is another option. The results of the DRCR Network study comparing the three anti-VEGF agents for DME revealed a higher visual gain with aflibercept at 1 year especially in eyes with worse visual acuity at presentation.[7] The mean letter gain was 18.9 letters with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab. This leads one to believe that eyes with severe disease and poorer vision such as those with chronic DME might respond better to aflibercept than either ranibizumab or bevacizumab. The possible efficacy of aflibercept over bevacizumab or ranibizumab failure may be explained by the fact that aflibercept binds not only VEGF-A but also VEGF-B and placental growth factor (PlGF). The role of PlGF in the pathogenesis of DME is not clear, but high levels of PlGF were seen in the vitreous in diabetic retinopathy. It is postulated to facilitate the breakdown of the blood–retinal barrier.[8]

In their study, Salimi *et al*. have shown substantial anatomical improvement with respect to reduced central retinal thickness, reduction in intraretinal cystic spaces as well as improvement in the ellipsoid zone in patients with chronic non-responsive DME who were switched to aflibercept.[9] This encouraging result was seen despite the very long duration of DME in their series. The mean number of bevacizumab injections prior to switch was 16.8 and the mean duration of treatment was 3 years.

The 29% decrease in central foveal thickness after switching to aflibercept was translated into a 4 letter gain in this study. Even this very modest visual gain might prove to be clinically acceptable and even welcome in these therapeutically challenging eyes. However, it is worth pondering whether a modest gain of 4 letters justifies the significant increase in the cost of the treatment. Most of the diabetic population in India is financially challenged and would not be able to afford the significantly higher treatment burden with repeated aflibercept injections. Moreover, aflibercept was not approved for DME treatment in India until recently. Just 2 weeks ago, the approval was given to Bayer following the completion of a clinical trial. Patient support programs are being considered by Bayer to reduce the financial burden. Nevertheless, it is certainly encouraging to have evidence of possibility of improvement in such chronic DME eyes.

The most suitable time to switch the anti-VEGF agent is still under debate. Some advocate early switching before permanent structural damage is seen due to persistent chronic macular edema. The long term visual outcomes are likely to be better in such patients. On the other hand, some patients who show poor response in the beginning might improve with continued treatment. A subgroup of late responders was identified in the BOLT study, and it was suggested that persistent macular edema at 4–12 months should not be a criterion to stop the treatment.[10] Salimi have shown benefit even if the switching was late and despite a very long standing chronic macular edema.[9]

In the real-world scenario, the patients do not receive regular monthly injections. Compliance to the treatment is a major hurdle. More often than not these patients would not have followed any treatment regimen and might have been under dosed leading to persistent edema. Presence of an epiretinal membrane, vitreomacular traction, or macular ischemia can also cause the DME to be non-responsive to anti-VEGF. It would be prudent to rule out these conditions before switching the agent. Furthermore, it is not necessary to "treat until dry". Eyes with stable OCT and stable vision on two consecutive visits can be watched further without additional treatment.

To conclude, eyes with chronic DME, non-responsive to bevacizumab even after 3 injections over 12 weeks, can be considered for switching. Aflibercept can be the chosen agent for switching in such chronically affected eyes.

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