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Editorial – Suboptimal response to intravitreal anti-VEGF treatment for patients with diabetic macular edema: is there any point in switching treatment?

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Abstract. – To investigate if there is any point in switching treatment in patients with diabetic macular edema (DME) showing suboptimal response to anti-vascular endothelial growth factor (anti-VEGF) treatment.

The standard of care for DME is anti-VEGF agents. Although anti-VEGF agents seem to be effective for the treatment of DME, there is a proportion of patients, showing a suboptimal response to anti-VEGF treatment. In such patients, switching treatment to another anti-VEGF agent or to intravitreal dexamethasone implant may provide favorable anatomical and functional results. However, without a control group, it is impossible to compare the effect of switching treatment with the effect of continuing the original administered treatment.

Switching treatment in patients with DME remains challenging. Further studies with a control group are needed to reach a safe conclusion.

Key Words:
Anti-VEGF, Diabetic macular edema, Dexamethasone, Treatment.

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetes mellitus, affecting about 20% of patients with diabetic retinopathy[1]. DME results from blood-retina-barrier disruption as a response to chronic hyperglycemia and to alterations in several biochemical pathways, leading to vascular leakage, fluid accumulation and macular thickening[2]. For many years, standard care for DME was focal/grid laser photocoagulation along with medical control of diabetes, blood pressure control and lipid management[3]. The identification of the pathophysiology of DME, particularly the role of vascular endothelial growth factor (VEGF) and inflammation, led to the development and use of intravitreally delivered agents, targeting to the afore-mentioned pathophysiological pathways[2].

Nowadays, the treatment of choice in DME is intravitreal anti-VEGF agents, i.e., ranibizumab (Lucentis, Novartis, Switzerland), aflibercept (Eylea, Bayer Healthcare, Germany) and bevacizumab (Avastin, Genentech, San Francisco, CA, USA). Each of these drugs has been tested in large, multicenter, randomized clinical trials and found to be safe and effective, showing improvement in visual acuity (VA) and reduction of macular thickness in patients with DME[4-8]. Protocol T was the first head-to-head randomized clinical trial, including 660 patients with VA impairment due to DME, comparing the three anti-VEGF drugs, and showing that all three agents presented VA improvement from baseline to 2 years with a decreased number of injections. In addition, anatomical and functional outcomes were similar between patients treated with aflibercept or ranibizumab, while aflibercept was superior to bevacizumab in terms of VA improvement[9].

Although all three anti-VEGF agents were effective for the treatment of DME, there is a proportion of patients who do not achieve optimal response to these agents, presenting refractory or persistent DME. Specifically, in protocol T, focal/grid laser photocoagulation was administered in 41%, 64% and 52% of patients treated with aflibercept, bevacizumab and ranibizumab respectively[9]. Furthermore, a post-hoc analysis of the Diabetic Retinopathy Clinical Research Network's Protocol I demonstrated

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that after 3 months of intravitreal ranibizumab treatment, about 40% of eyes showed suboptimal VA response (gain < 5 letters) and had poorer long-term visual outcomes than eyes with pronounced early response (gain > 10 letters)[10]. In such patients with suboptimal visual response after the first 3 intravitreal anti-VEGF injections, it may be appropriate to consider adjustments to the treatment regimen and a reasonable option could be to switch treatment from one anti-VEGF agent to another.

Previous studies have evaluated switching treatment between anti-VEGF agents, showing variable results. Change from bevacizumab to ranibizumab in patients with refractory DME presented significant reduction in central retinal thickness and improvement in VA, which did not reach significance in the majority of cases[11-13]. Accordingly, change from bevacizumab/ranibizumab to aflibercept resulted to significant improvement in macular thickness and stabilization or improvement in VA[14-21]. However, these studies had short follow-up time (1-3 months) and lack of control group, while there are no consistent switching rules among studies.

On the other hand, since inflammation plays a significant role in the pathogenesis of DME, intravitreal steroids have been shown to be useful in the treatment of DME, as they inhibit inflammation, leukostasis and phosphorylation of cell-junction proteins, as well as they block the production of VEGF and other inflammatory mediators in DME[22]. Of note, a recent meta-analysis found that treatment with intravitreal dexamethasone implant is associated with significant improvement in VA and suggested clinicians to have a multimodality approach when treating DME, using this treatment option especially in those, who have a suboptimal response to anti-VEGF therapy[23].

Nevertheless, it should be noted that without a comparison group, it is impossible to know whether the improvement, which is observed after switching is related to the new treatment or could be attributed to "regression to the mean" or "time effects" phenomena[24]. Ferris et al[24] investigated the course of eyes in CATT and DRCR.net participants for age-related macular degeneration and DME respectively, that met typical criteria for switching treatment, but did not have a change in treatment and continued the original therapeutic agent. The authors found that there was a 3- to 5- letter improvement in mean VA and a mean 40-70 μm reduction in central retinal thickness over the 3 months[24]. Additionally, another study, trying to determine the ideal time-point at which it is best to define suboptimal response after ranibizumab treatment for DME based on real-life data, demonstrated that patients with suboptimal response may present improvement with continuous ranibizumab treatment, without any switch[25]. An interesting point that should be addressed is the optimal time-point when switch from one anti-VEGF to another treatment should be performed. The EARLY analysis of DRCR.net protocol I suggested month 3 as a potential time-point for switching[10], while other studies set months 3 or 4 as time-points for switching, after completing the loading phase of 3 or 4 intravitreal injections[12,18]. Moreover, month 12 could be also considered as a time-point to define suboptimal response[25].

Taken as a whole, all anti-VEGF agents seem to be effective for the treatment of DME, although there is a proportion of patients showing suboptimal response to anti-VEGF treatment. In such patients, adding laser treatment, as well as switching to either another anti-VEGF agent or to intravitreal dexamethasone implant may provide favorable anatomical and functional results. However, without a control group it is impossible to compare the effect of switching treatment with the effect of continuing the original administered treatment.

Conclusions

Further large randomized, controlled studies are needed to scrutinize the optimal time-point for switching anti-VEGF treatment and to evaluate switching to anti-VEGF or intravitreal dexamethasone implant in patients who do not respond to anti-VEGF treatment. A control group of patients continuing the originally administered agent needs so as to obtain reliable results.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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