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EDITORIAL

The role of steroids in treating diabetic macular oedema in the era of anti-VEGF

Tamir Weinberg[1,2] · Anat Loewenstein[3,4]

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The prevalence of diabetes is increasing worldwide and with it its possible visual impairing sequelae [1]. Diabetic macular oedema (DMO) remains the main cause of visual impairment.

Although the pathogenesis of DMO is not fully understood, it involves three main components [2]. Vascular component, mediated by vascular endothelial growth factor (VEGF) including microaneurysms development and breakdown of blood–retina barrier. An inflammatory process in which pro-inflammatory proteins lead to capillary degeneration and pericyte loss. There is also a neurodegenerative process contributing to the pathological cascade.

Why then steroids, targeting the inflammatory part, should not be part of our armamentarium in treating DMO. According to recent PAT survey of the ASRS, over two thirds of ophthalmologists worldwide choose anti-VEGF as their first line of treatment of DMO [3]. By combating inflammatory cytokines, steroids have at least a theoretical role in the management of this disease.

Moreover, as has been shown by the Diabetic Retinopathy Clinical Research Network (DRCRnet) protocol I and protocol T, over 40% of patients still had persistent DMO despite adequate treatment with anti-VEGF [4, 5].

We have identified some subgroups of patients with DMO in whom steroids should be considered over the course of their disease management.

Non-responding patients

As mentioned, 40–60% of patients treated with an anti-VEGF will have persistent oedema after an intensive treatment of six monthly injections, in these patients, visual acuity (VA) will not be as good as in the group without persistent oedema [4, 5].

Non-compliant patients

Widespread use of anti-VEGF agents has achieved a robust improvement in VA. Nevertheless, in order to achieve these improvements, patients have to be treated aggressively in the first year as has been shown in the pivotal trials. In the DRCRnet protocol T, the median numbers of injections in year 1 were 9, 10, and 10 in the aflibercept, bevacizumab, and ranibizumab groups, respectively. In the following year, the injection number needed was reduced to 5, 6, and 6 injections [6]. In real world, the actual number of injections is much smaller and consists of 4.3 injections in the first year, and a much lower number in subsequent years [7]. As a result, VA outcome is lower in real life as compared with the pivotal trials. In order to avoid a less than optimal VA improvement in non-compliant patients, a slow release steroid implant may serve as a viable option.

Pregnant women

Despite lack of large prospective studies, it is suggested that due to the important role of VEGF in the development of the foetus, a potential damage may be inflicted to the foetus when using anti-VEGF. Several case series demonstrated a correlation between anti-VEGF injections to spontaneous miscarriages and preeclampsia when given at the first five weeks of gestation [8, 9].

✉ Tamir Weinberg
tamirw1@netvision.net.il

[1] Hadassah School of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

[2] Department of Ophthalmology, Kaplan Medical Center, Derekh Pasternak, Bilu Junction, PO box 1, Rehovot, Israel

[3] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[4] Department of Ophthalmology, Tel Aviv Medical Center, Tel Aviv, Israel

Patients with recent arterial thromboembolic events (ATEs)

The question whether intravitreal anti-VEGF agents increase the chances of ATEs is still under debate. In most randomized clinical trials [6, 10–12], patients with recent myocardial infarction or cerebrovascular accident were excluded from the study and by so, reducing the ability of the study to correctly asses the safety in this subgroup of patients. Systemic review and meta-analysis showed conflicting results. Thulliez et al. concluded that the studies and meta-analyses were not powered enough to correctly assess these risks [13], while Avery et al. did suggest a possible increased risk for ATEs [14].

In addition to these types of patients there are a few ocular findings in which the use of steroids has been claimed to be beneficial.

Patients with hard exudates (HE) at the centre of fovea

A postulated predictor of VA outcome is the presence of HE, which may correspond to a less favourable VA outcome [15]. A post hoc analysis of the Bevordex study, comparing monthly bevacizumab to dexamethasone (DEX) implant every 16 weeks, demonstrated the different effect of these drugs on the regression of HE. This study showed that both groups resulted in decrease of the total area of HE but also showed a non-significant trend at 24 months in which more DEX-implant treated eyes had complete clearance of HE. There was greater regression of HE from the fovea centre in the DEX-implant treatment group, which was statistically significant at 12 months but no longer at 24 months [16].

Pseudophakic patients

In large clinical trials studying the effects of intravitreal steroids in treating DMO, pseudophakic eyes were shown to have better VA outcomes compared with phakic eyes, namely the DRCRnet protocols B, I, U and the MEAD study group [17–20]. Because steroids accelerate cataract formation, we are less reluctant to use steroids in pseudophakic patients.

Vitrectomised eyes

It has been previously suggested in animal model by Chin et al. that the vitreous body may serve as a reservoir that helps prolong the therapeutic duration of medication administered intra-vitrealy [21]. Therefore, vitrectomised eye may benefit less from the therapeutic effect of an injected drug. In the Champlain study group, a single injection of DEX-implant was given, and patients were followed up for 26 weeks [22]. Overall at week 8, about 30% of patients gained ≥10 letters suggesting the advantage of a slow release DEX implant.

Is there a role for a combination therapy?

In the DRCRnet, protocol U, pseudophakic patients with persistent DMO showed better VA outcome with combination treatment of ranibizumab and DEX implant compared with ranibizumab alone [20].

Given the above data, one cannot overlook the benefits of steroids when treating DMO with their ability to induce a longer therapeutic effect when given as an implant or insert and their relative safety in given circumstances in which anti-VEGF use is warranted.

New drugs emerge with pronounced anti-inflammatory effect like faricimab (Roche, Genentech) targeting both angiopoietin-2 and VEGF-A [23] and drugs with longer duration of action such as brolucizumab (Novartis) [24], and abicipar pegol (Allergan) [25]. New slow release devices such as the port delivery system will enable us to reduce the number of injections. Patient screening using artificial intelligence and deep learning will be more commonly used in the near future.

All these innovations may remodel the treatment paradigms for DMO. However, until these become available, patients may still benefit from steroids in the treatment of DMO.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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