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RESEARCH ARTICLE

When to Perform a Treatment Switch in Diabetic Macular Edema in Patients with Inadequate Response to Anti-VEGF

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ABSTRACT

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients. Multiple therapeutic options are currently available for these patients, including laser photocoagulation; intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs or steroids; or pars plana vitrectomy for tractional DME. The initial treatment for DME is well-defined and widely accepted, with anti-VEGF as first-line option. Nevertheless, between 30 and 40% of patients show partial response or no response whatsoever. There is no consensus on the number of injections needed in order to classify a patient as a non-responder or sub-optimal responder, nor on the definition of the latter. In this study, these concepts are analysed as well as the different therapeutic alternatives at hand, with special interest on the switch between different anti-VEGF and/or steroids. These analyses are performed from an anatomical and functional point of view as well as from an economic, cost-effectiveness perspective. Recent evidence suggests that an early switch to dexamethasone implant in eyes that did not respond adequately to anti-VEGF therapy after 3 injections provides better functional outcomes while alleviating the heavy economic burden of this disease.

Keywords: macular edema, diabetic retinopathy, dexamethasone, anti-VEGF

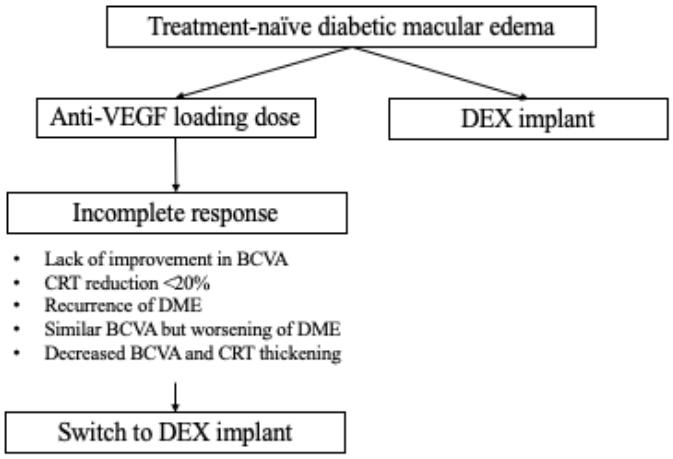
1. Introduction

The prevalence of diabetes mellitus (DM) worldwide is in a frightening, continuous rise that currently sits at 425 million people and is projected to affect 430 million by the end of the decade and more than 600 million by 2045.[1,2] More than 30% of diabetic patients develop microvascular complications derived from an increased oxidative stress and inflammation caused by hyperglycaemia. In the specific case of diabetic retinopathy (DR), the first clinical signs are the appearance of saccular dilations of capillary walls called microaneurysms and microhaemorrhages, and the disease can potentially evolve to a sight-threatening proliferative stage where neovessels spread throughout the retina and anterior segment of the eye.

The most common cause of visual acuity (VA) loss in DR patients is the appearance of diabetic macular oedema (DME), that affects nearly 7% of diabetic patients,[3] and can cause a significant impact in patient's quality of life.[4] Persistent DME leads to photoreceptor damage, and should be managed promptly to prevent irreversible visual decline. It is clinically identified as central retinal thickening via accumulation of fluid caused by the loss of the blood-retinal barrier. Its pathogenesis is complex and several factors come into play in the process such as hypoxia, ischemia, upregulation of certain pro-inflammatory molecules like vascular endothelial growth factor (VEGF), tumour necrosis factor-α (TNFα), nitric oxide or interleukins (IL) 1B, 6 and 8.[5]

2. Current treatment for DME

Treatment algorithms for DME have evolved over time and appear summarized in Table 1. Laser photocoagulation showed visual improvements, ability to resolve macular oedema and a reduction of vision loss rates compared to placebo in the ETDRS study and was the main treatment for DME for over two decades.[6,7] But, while most of the patients were treated with laser photocoagulation as a first-line option not so long ago,[6,8] intravitreal therapies have become the go-to choice for most clinicians nowadays according to the guidelines published by the European Society of Retina Specialists (EURETINA)[9]. While RISE&RIDE and VIVID&VISTA studies support the use of ranibizumab (Lucentis, Genentech, San Francisco, CA, USA) and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) respectively for the treatment of DME, bevacizumab (Avastin, Genentech, San Francisco, CA, USA) has been used off-label with good results as a more economically-accessible choice. Similarly, steroid intravitreal injections have evolved since the first studies that evaluated the efficacy and safety of triamcinolone acetonide,[10,11] proving to be an effective treatment, even on par with ranibizumab in pseudophakic patients.[12] Corticosteroids curb the expression of some important cytokines involved in DME pathogenesis including VEGF, and also prevent leukostasis and retinal leakage.[13] Unlike anti-VEGF drugs, long-lasting options have become available with the development of slow-release formulations of dexamethasone (Ozurdex, Allergan Inc., Irvine, CA, USA)[14] and fluocinolone (Iluvien, Alimera Sciences Inc., Al- pharetta, GA, USA),[15] with good anatomical and functional results and better safety profiles than previously used intravitreal steroids.



But despite the fact that both anti-VEGF and steroids have demonstrated good rates of safety and efficacy, more than 96% of retina specialists in Spain still consider anti-VEGF drugs as their first-line approach.[16] This could still be justified by the higher rates of secondary cataract progression and the potential development of glaucoma in patients treated with steroids when compared to anti-VEGF drugs, which are only contraindicated in the case of recent stroke, myocardial infarction and pregnancy. The long-lasting effect of dexamethasone and fluocinolone, however, makes them a good choice for patients that do not comply to clinic visits, bearing in mind that they provide non-inferior results and less injections needed per year when compared to bevacizumab.[17]

The scarcity of clinical trials comparing the efficacy of different current treatment options and regimens for DME justifies the lack of consensus over the treatment algorithm to apply in these patients. Only ranibizumab and aflibercept have proven to be superior than macular laser, but there is no clear evidence comparing the effects of ranibizumab/aflibercept *vs.* dexamethasone/fluocinolone, taking into consideration the different treatment regimens that may apply, so the final drug choice is influenced or determined by the specific type of oedema, patient's response, specialist's preference and even economic or regulatory reasons of each centre or health system.

3. Anti-VEGF treatment for DME

Monthly treatment with anti-VEGF is a very effective choice with randomized trials showing good results over two years.[18,19] But maintaining this kind of regimen can be really challenging real-life, daily clinical practice. In this sense, *pro re nata* (PRN) treatment schedules after achieving an anatomical response have shown to maintain visual acuity level over the course of 5 years, needing less injections, as the Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol 1 shows.[20] Treat and extend regimens (TER) offer

another option for the management of DME, adapting and increasing the intervals of treatment according to patient's response after achieving an optimal outcome with monthly injections. TER has been shown to be no different to PRN regarding VA gains, reducing the number of clinic visits by 40%,[21] and seemingly showing a more stable evolution and fewer recurrence rates.[22]

But in spite of the good results obtained using anti-VEGF for DME, there are still patients that do not show the expected response, with up to 40% of patients suffering from persistent macular oedema after two years of treatment with ranibizumab, according to a DRCR.net study.[23] A post-hoc analysis of said study reported that patients that gained 5 letters or less after treatment with 3 anti-VEGF injections had inferior long-term outcomes in terms of VA,[24] which occurred in 40% of cases. In addition to this, a continued treatment for two years did not lead to better results in terms of central retinal thickness (CRT) or VA.[23]

These reports have important implications for retina specialists' daily practice as mid to long-term response to ranibizumab could be revealed by early anatomical results obtained.[25] Anatomical non-responders are defined by a reduction of CRT <20% after 3 to 5 anti-VEGF intravitreal injections. Meanwhile, patients are classified as functional non-responders in case they fail to gain 5 ETDRS letters after the same period. Functional and anatomical response are not bound together in all cases.[26] On one hand, there are patients that show a CRT reduction >20% that does not translate into best corrected VA (BCVA) gains. Such cases should be studied in detail as macular ischemia, outer retinal damage or foveal exudate accumulation, among others, may be responsible for the lack of improvement. On the other hand, there are patients that show good functional results with sub-optimal anatomical response.

4. Beyond anti-VEGF therapy

So patients that do not adequately respond to a certain anti-VEGF could potentially benefit from other treatments, in the form of a different anti-VEGF or a steroid. MEAD trials evaluated the long-term efficacy of intravitreal dexamethasone (DEX) in the treatment of DME. After 3 years, a significant improvement in DME compared to sham controls and delayed progression in diabetic retinopathy severity was observed.[13,14] Literature on anti-VEGF switch is mostly limited to retrospective studies where solid conclusions can hardly be drawn. Most of them report anatomical improvements that can be related to the treatment intensification frequently associated with the switch, whereas only a few of them report better functional results, probably due to the effects of long-standing oedema.[26] Patients suffering from long-standing DME can potentially develop irreversible changes that limit their VA gains, so cases that do not adequately respond to anti-VEGF should be considered for a switch to intravitreal steroids, with studies that suggest that intravitreal dexamethasone could provide improvements in eyes that did not respond to a loading dose of at least 3 anti-VEGF injections.[27–30]

Busch *et al.* compared the anatomical and functional response of continued anti-VEGF treatment vs. switch to DEX in a retrospective, multicentric case-control study in patients with persistent oedema after three anti-VEGF injections. They reported better functional and anatomical results in switched patients than in those that stayed on anti-VEGF therapy.[28]

Hernandez Martínez *et al.* conducted a retrospective study comparing the effects of early vs. late switch to DEX in 69 DME eyes with sub-optimal response to anti-VEGF regarding BCVA and CRT. They concluded that patients switched to DEX after 3 injections showed better anatomical and functional results than those switched after 6 or more anti-VEGF injections.[27]

Our group recently published a real-life, retrospective study where DME patients with insufficient response to anti-VEGF were switched to DEX implant.[30] Sub-optimal response to anti-VEGF treatment was defined by: (1) lack of improvement in BCVA; and/or (2) a CRT reduction < 20%; and/or (3) recurrence of DME despite monthly anti-VEGF injections; and/or (4) similar BCVA but worsening of DME; and/or (5) decreased in BCVA and a CRT thickening. Patients were divided in 3 groups: 1. Naïve patients; 2. Eyes that received 3 intravitreal anti-VEGF injections before the study; and 3. Eyes that received >3 intravitreal anti-VEGF injections before the study.

The results obtained in this study suggest that switching to DEX implants in patients with a sub-optimal response to anti-VEGF drugs was associated with greater gains in terms of BCVA when the switch took place after a loading dose of 3 anti-VEGF injections, rather that in those who received more than 3 injections. Nevertheless, it has to be noted that both groups showed anatomical improvements in the shape of a CRT reduction ≥20% in more than 80% of cases.[31] Both previously treated eyes and naïve showed statistically significant improvements in terms of BCVA, with no differences between groups. Both groups showed statistically significant reductions of CRT as well, and this reduction was significantly greater in naïve eyes at 1 year follow-up.

Bearing in mind the results from these studies and taking a close look at the early anatomical results obtained after treatment with anti-VEGF could help us select which patients could benefit from an early switch to intravitreal steroids that would potentially help them reach better functional outcomes with better BCVA.

5. Economic analysis of the switch to intravitreal steroids

Recently, a study on a theoretical economic model on the response of DME to treatment with intravitreal injections of anti-VEGF[32] based on the results found in Protocol T,[33] reported and calculated the cost generated after treatment of patients with DME with central involvement and loss of vision, to identify anti-VEGF responders after 6 injections that were not considered responders after only 3 injections.[32] On this matter, it has been suggested that extending the loading dose for DME patients could result in a higher response rate at the end of a six-month induction period.[23,34] However, identifying these new responders would imply treating all patients regardless of whether they ultimately respond to treatment or not, given that there are no reliable biomarkers of anti-VEGF response.[35]

From an economic point of view, this analysis revealed that a minimum investment of almost 6,000 € is required to identify an additional responder patient, and depending on the anti-VEGF agent used this cost could increase up to 10,000 €.[32] Although there is no consensus on the anti-VEGF induction period needed for DME, the results of this analysis provide additional information on the pharmaceutical costs generated by performing a prolonged loading dose of 6 months, in patients who do not respond after 3 monthly injections. We define the switch after 3 monthly injections as an "early switch".[9]

Patients with a suboptimal response can be switched to a different anti-VEGF agent, but there is also the possibility to select a treatment with a different mechanism of action and switch to a DEX implant with good anatomical and functional results.[36] On this regard, DEX may be a reasonable option in patients with refractory DME.[37] Additionally, in patients with a limited or insufficient early response after 3 monthly injections in BCVA or CRT, the switch

from anti-VEGF to DEX led to a 3-5-fold improvement compared to anti-VEGF responders.[38]

6. When to perform the switch

Depending on the patient profile, DEX implant can be considered as a possible alternative or even a preferred choice over anti-VEGF therapy. Many factors can influence this decision, including presence of inflammation biomarkers, preferential or alternative indications, time to retreatment, efficacy and safety aspects.[39]

However, to determine the best time to switch treatment, not only clinical outcomes should be considered, but also the eventual economic impact. Published studies on DME on this matter have been performed in similar populations and therefore similar responses can be expected.[28,40–45] First, a multicentre study performed in the United States that included patients treated with the 3 available anti-VEGF drugs, with a mean age of 63.4 years and 80.8% with type 2 diabetes. The mean BCVA was 11.8 lines (59 letters), and mean CRT was 414 µm.[40] A different single-centre study, also performed in the US, included anti-VEGF-treated patients with a mean age of 67.83 years, a mean BCVA of 0.6 log MAR (55 letters), and a CRT of 434.58 µm.[41] Finally, a multicentre study conducted in Australia and several European countries in which the majority of enrolled patients had type 2 diabetes, with a mean age of 62-65 years, mean BCVA of 64-67 letters and mean CRT of 407-433 µm.[42]

In addition, European studies include patients with similar characteristics. A multicentre study conducted in France, included patients treated with anti-VEGF with a mean age of 66.1 years, 83.5% had type 2 diabetes. Mean BCVA was 59.2 letters and mean CRT 457 µm.[43] In Spain, a retrospective study that included patients treated with ranibizumab and aflibercept, reported a mean age of 69 years, 90% type 2 diabetes, mean BCVA of 0.52 log MAR (60 letters) and mean CRT of 456 µm.[44] Notably, all of these patients across the different studies display similar characteristics, and treatment decisions are comparable between the United States and Europe, and are in accordance with the current recommendations and clinical guidelines for the treatment of DME,[9,46] except the use of steroids.[9,46]

Although a six-month induction period of monthly injections is recommended by several clinical guidelines, clinicians may choose a different treatment regime based on the economic impact of treatment, and this could eventually result in lower cost per additional responding patient, depending on the results obtained. García Layana *et al.* reported the results of the use of the DEX implant for the treatment of DME using a Delphi approach.[47] The panel of experts agreed on the need of switching to DEX implant in patients who do not respond after a maximum of 3 anti-VEGF injections. However, there was no consensus on when to perform the switch to anti-VEGF therapy in patients who do not respond sufficiently to DEX implant. [47]

7. Ecomonic implications of early VS. late switch

Remarkably, a budget impact analysis compared the first 3 years of DEX implants' market with a scenario where only anti-VEGF were available. The results of this analysis showed cost savings mainly due to the fewer number of DEX injections needed. [48] As stated before, our group reported the results obtained in 129 eyes with DME and insufficient response to anti-VEGF, and the early switch to DEX at 3 months provided better functional results compared with the switch to DEX performed after more than 3 anti-VEGF injections. [31] Consequently, the need to extend anti-VEGF therapy in those subjects with insufficient response after 3 anti-VEGF injections is under debate.

Albeit the proven benefits of anti-VEGF therapy on functional and anatomic outcomes, some patients do not manifest a sufficient response to this therapy.[19,49] Hence, the switch to DEX implant can lead to better anatomic results than anti-VEGF extended therapy. [28,50,51]

As previously mentioned, the study by Busch *et al.*[28] compared treatment with anti-VEGF *vs.* switch to DEX implant after 3 initial injections of anti-VEGF, in eyes with eyes with persistent DME. Patients switched to DEX obtained better functional and anatomical results.[28] Similarly, Hernandez-Martinez *et al.*[27] demonstrated that the early switch after 3 injections was associated with better functional outcomes compared with the late switch, with equivalent anatomic results in both groups. Although in our study we did not find any significant differences regarding anatomic results,[31] eyes receiving 3 anti-VEGF injections reached a significantly better BCVA, both in absolute numbers and percentage, compared to those receiving more than 3 anti-VEGF injections.

Even though from the clinical perspective the DEX implant could achieve good anatomic results in those eyes which did not respond adequately to more than 3 anti-VEGF injections, we should consider the economic impact of extend "too much" a "non-completely efficacious therapy". According to a Spanish multicentric study, the total cost of DME per year, including diagnosis, medical treatment and loss of labour productivity related to timework loss raises to around 19,000 €,[52] with an estimated cost of anti-VEGF medication/year of around 7,000 €.[53]

Functional and anatomic improvement observed in our study is in agreement with current scientific data available in the literature.[54–61] Regarding the number of DEX implants administered in our study, no significant differences were found between naïve and treated eyes (1.8 ± 0.6 compared to 1.6 ± 0.7 implants, respectively) or between eyes treated with three anti-VEGF injections or those receiving more than three injections (1.5 ± 0.7 *vs.* 1.7 ± 0.8 implants, respectively).[31]

The cost of each implant is 1,050 € and the treatment response rate in DME patients treated with DEX implant is close to 90%;[28,62,63] D. Bellocq *et al.* found 87%,[62] Matonti *et al.* 95.7% from which 21.7% were naïve[63] and Busch *et al.* 90%, with 35% of non-responders.7 Based on the theoretical model of the T protocol in our series of 546 patients, the cost would have been of 1,228 € per responder patient, and 602,000 € in total. For all the patients treated with anti-VEGF (n=546), an estimation of 7,927.02 € (13.7 injections) would need to be invested per additional responder patient,[32] and the total cost would raise up to 4,328,152.92 €.

Our study has some limitations that need to be addressed. First, the retrospective design could have led to a selection bias and confounding factors might have influenced our results.[31] Another limitation is that we did not include other clinical variables that may have interfered with the functional outcomes of our patients. For instance, a recent study by Zarranz-Ventura et al. with 2,736 eyes and 6,015 injections, reported an incidence of cataracts in 576 eyes (32.5% of phakic eyes) requiring surgery. Therefore, we believe that this fact should be considered in a cost analysis.[64]

8. Conclusions

Despite the aforementioned limitations, the results of this study combined with the pharmacoeconomic data, suggest that in eyes that did not respond adequately to anti-VEGF therapy after 3 injections, the switch to DEX implant provided better functional outcomes, with theoretically remarkable cost savings. Importantly, the early switch to DEX could represent the best option, especially in pseudophakic patients, and should be also precisely considered in phakic patients.

Due to the recent COVID-19 pandemic, the need to reduce the heavy burden of intravitreal injections has become a mandatory issue to be addressed. In this sense, the prompt identification of patients with DME who will benefit from a single intravitreal injection of DEX instead of monthly injections of anti-VEGF, could be of great importance to reduce the hospital injection burden.[65] Therefore, the treatment of eligible subjects with DME could help reduce the great burden of repeated intravitreal injections for patients and for the healthcare system.[35]

Prospective, randomized and multicentre studies analysing when would be the best time to perform the switch from anti-VEGF to DEX in patients with incomplete or no response to anti-VEGF, assessing not only clinical but also economic variables are mandatory. This could help us optimize resources and workforce to deliver the best possible treatment to our patients.

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Author contribution: JMRM and JRM designed the study and contributed equally in data acquisition, data analysis and interpretation; JMRM, JRM and LGB contributed drafting or revising the manuscript critically; agreed to submit; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Data availability statement: Data are available upon request to the corresponding author.

Conflicts of interest: JMRM: advisory board of Allergan, Bayer and Novartis. The rest of the authors have no conflicts of interest to disclose.

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