Current Opinion on Long-Lasting Therapy in CI-DME

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Abstract: Diabetes has been recognized by the World Health Organization (WHO) as a noncommunicable, chronic disease and a 21st century epidemic. Diabetic retinopathy (DR) is one of the three leading causes of blindness among the working-age population aged 20 to 74 years.

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients, and the impact of DME on quality of life is very significant. Currently, first-line treatment recommendations for center-involved DME (CI-DME) include intravitreal anti-VEGF injections on a monthly or bimonthly regimen. It is essential to understand the burden that treatment regimens have on patients, as well as on healthcare systems. The most significant improvement to the regimen would be to have fewer injections and monitoring visits while maintaining satisfactory vision outcomes. A lower number of intravitreal injections could optimize disease outcomes by improving patient compliance.

This article discusses novel agents targeting alternative pathways and mechanisms involved in the pathogenesis of DME, as well as high-dose drugs and novel approaches to treatment regimens aimed at extending treatment intervals, decreasing treatment burden, and increasing treatment efficacy. This knowledge will enhance the selection of treatments, thereby improving patient compliance with therapy and optimizing healthcare system resources.

Keywords: Diabetes, Diabetic retinopathy, Diabetic macular edema, Anti-VEGF, Intravitreal injections, Treat and extend, Steroids.

INTRODUCTION

Diabetes has been recognized by the World Health Organization (WHO) as a noncommunicable, chronic disease and a 21st century epidemic. Between 2000 and 2019, there was a 3% increase in diabetes mortality rates by age. Based on the prevalence data provided by the International Diabetes Federation (FDA), in 2030, the number of diabetic patients is expected to increase to 522 million, and in 2045, it is expected to increase to 700 million worldwide [1]. Diabetic retinopathy (DR) affects approximately 30% of diabetes patients. After 20 years of diabetes, approximately 99% of patients with type 1 diabetes and 60% of patients with type 2 diabetes have features of diabetic retinopathy [2, 3]. Moreover, in the working-age population aged 20 to 74 years, diabetic retinopathy (DR) is one of the three leading causes of blindness [4].

Diabetic macular edema (DME) can develop regardless of the stage of diabetic retinopathy. DME is classified as either center-involved DME (CI-DME) or non-center-involved DME (NCI-DME). The International Council of Ophthalmology (ICO) defines NCI-DME as retinal thickening in the macula that does not involve the central subfield zone and that is 1 mm in diameter. CI-DME refers to retinal thickening in the macula that does involve the central subfield zone and that is 1 mm in diameter [5].

The prevalence data vary across the globe, which can be attributed to ethnicity and genetic predisposition but also to disparities in health care systems in different regions of the world. The Wisconsin Epidemiologic Study of Diabetic Retinopathy revealed that after 10 years of follow-up, 20% of patients with diabetes type 1 and 25% affected type 2 diabetes developed DME [2, 3]. A meta-analysis of 35 studies performed between 1980 and 2009 across four continents estimated the overall prevalence of DME as 7.5% [6]. A DME prevalence of 3.7% and a pooled mean annual incidence of 0.4% (95% CI 0,5–1,4%) were reported in a large European meta-analysis with a sample size of 205 743 individual [7].

DME is the most common cause of vision loss in diabetic patients, and the impact of DME on quality of life is very significant. Sivaprasad S. *et al*. reported that 70% of DME patients report a moderate to large impact on perceived quality of life compared to patients with other chronic conditions, such as central retinal vein occlusion, diabetes, asthma, glaucoma, hypertension and thyroid disease [8]. It is fundamental to understand the burden that treatment regimens have on patients

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and on health care systems. Currently, first-line treatment recommendations for CI-DME include a monthly or bimonthly regimen of intravitreal anti-VEGF injections. This causes a high treatment burden. Additionally, the majority of patients with diabetes have at least one comorbidity, and up to 40% of patients have at least three comorbid diseases [9]. Sivaprasad S. *et al*. estimated that in Europe, a 6-month period was associated with approximately 20 hours of appointment burden per DME patient. For the above reasons, nonadherence to DME treatment and follow-up regimens is a common problem and reduces clinical treatment outcomes under real-life circumstances compared to randomized clinical trials (RCTs). Moreover, patients with DME have the highest risk of patient-associated nonadherence and are thus associated with a higher risk of significant vision loss than patients with age-related macular degeneration (AMD) and branch retinal vein occlusion (BRVO) [10-12]. Furthermore, it is worth emphasizing that due to aging populations, the increased prevalence of diabetes and the longer duration of diabetes, DME has become an increasingly widespread public health problem. Considering all those data, an overall effort should be made to reduce the treatment burden for DME patients. The most significant improvement to the regimen would be to have fewer injections and monitoring visits while maintaining satisfactory vision outcomes. A decreased number of intravitreal injections could have the potential to optimize disease outcomes by improving patient compliance.

Novel agents targeting alternative pathways and mechanisms involved in the pathogenesis of DME, as well as high-dose drugs and novel approaches to treatment regimens, aim to extend treatment intervals, decrease treatment burden and increase treatment efficacy. This knowledge will improve the selection of treatments, thereby enhancing patient compliance with therapy and optimizing health care system resources.

CURRENT WORLDWIDE GUIDELINES ON DME MANAGEMENT

In terms of DME treatment, the landmark Early Treatment of Diabetic Retinopathy Study (ETDRS) published in 1985 revealed that moderate visual loss may be reduced by over half by performing laser photocoagulation (focal/grid) [13]. However, a true breakthrough was demonstrated in 2010, when the Diabetic Retinopathy Clinical Research Network (DRCR.net) reported the results of a multicenter randomized clinical trial (RCT) Protocol I, which evaluated the use of intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for the treatment of DME [14]. The main conclusion was that intravitreal ranibizumab with prompt or deferred laser is more effective through at least 1 year than prompt laser alone for the treatment of DME involving the central macula. Ranibizumab, a 48-kDa recombinant humanized monoclonal IgG1 antibody fragment (Fab) against VEGF-A, was approved by the U.S. Food & Drug Administration (FDA) for treating DME in 2012. Its effectiveness has been widely proven in RCTs (RESOLVE, REVEAL, RISE, RIDE) and real-life studies [15-20]. The main outcome of those studies relevant for practicing clinicians was that intravitreal ranibizumab treatment provides superior visual outcomes compared to conventional laser treatment. Subsequently, different anti-VEGF agents, including ranibizumab, aflibercept, and bevacizumab, were introduced as the first-line treatment options recommended worldwide [4, 13, 21-26]

Generally, available anti-VEGF can be classified into the following: monoclonal antibodies to VEGF (bevacizumab; off-label), antibody fragments to VEGF (ranibizumab, brolucizumab), and recombinant fusion proteins composed of the key VEGF binding domains from VEGFR-1 and VEGFR-2 fused to the constant region (Fc) of human immunoglobulin G1 (aflibercept, conbercept). Another treatment option is corticosteroid injections (dexamethasone or fluocinolone implants or triamcinolone). Triamcinolone is usually not recommended by the international guidelines for clinical use because it is not licensed for intravitreal injection. Additionally, the drug has a short duration and a different safety profile compared to intravitreally approved steroid implants (dexamethasone or fluocinolone).

The current management from international expert panels is summarized in Table **1**. Recommendations vary from very general (anti-VEGF, steroid, laser) to detailed, specific indications depending on the visual acuity (VA), lens status, central foveal thickness (CFT) or even disposition of patients to receive monthly injections (and/or come to scheduled visits) in the first 6 months of therapy. The majority of panels agree that anti-VEGF remains the first-line treatment with the intensive loading phase. Some guidelines include specific recommendations regarding the treatment regimen after the loading phase. The European panel advises continuing with a fixed schedule (bimonthly injections) or a PRN (pro-re-nata) regimen with monthly monitoring visits [25]. A similar approach is included in

Table 1: Current Worldwide Guidelines on CI-DME Management

	First Line Treatment	Second Line Treatment
Europe; the European Society of Retina Specialists: EURETINA Year: 2017 [25]	Anti-VEGF Aflibercept is the drug of choice in DME eyes with baseline BCVA below 69 letters. anti-VEGF treatment regimen: loading injections at 4-weekly intervals should be followed by a regimen of fixed bimonthly injections or a PRN regimen with monthly monitoring only. Steroids: history of a major cardiovascular event; not willing to come for monthly injections (and/or monitoring) in the first 6 months of therapy. Dexamethasone shall be used first; Fluocinolone may be appropriate for nonsteroid responders with chronic macular edema that is not responsive to other treatments. Triamcinolone should be used only in patients who cannot get the approved agents for this indication	Steroids after 3–6 anti-VEGF injections, depending on the specific response of each patient.
USA American Academy of Ophthalmology; AAO Year:2020 [24]	Anti-VEGF Focal/grid laser treatment. No detailed specific recommendations on the choice of anti-VEGF, nor the treatment regimen.	Anti-VEGF Steroids focal/grid laser treatment
Great Britain UK Consensus Working Group Year: 2020 [23]	The treatment regimen is dependent on CFT (above or below 400 µm) and the lens status of the patient. If CFT < 400 µm anti-VEGF are recommended in phakic patients and steroid implants in pseudophakic patients and cases of phakic patients with chronic DME, unresponsive or unsuitable for anti-VEGF, pregnant women, and in the event of recent cardiovascular comorbidities. If CFT > 400 µm anti-VEGF is recommended as the first line regardless of the lens status. A steroid may be used in patients with chronic DME, unresponsive or unsuitable for anti-VEGF, pregnant women, in the event of recent cardiovascular comorbidities, regardless of the lens status. VA <69 letters, consider anti-VEGF monotherapy with either aflibercept 2 mg or ranibizumab 0.5 mg as the first choice, as there is no difference in long-term outcomes with either drug. No specific recommendations on the choice of treatment regimen.	Steroid implants: Dexamethasone Fluocinolone Occasional adjunctive delayed laser treatment may sometimes be considered, especially where there are leaking microvascular changes away from the fovea that persists, despite regular anti-VEGF treatment.
Asia An Asian-specific guideline for DME treatment Year: 2018 [21]	Anti-VEGF therapy The choice of anti-VEGF agent depends on baseline VA In patients with worse VA (worse than 20/40), aflibercept may result in more rapid VA improvement compared with ranibizumab (0.3 mg) over 1 year, although this difference was not statistically significant in year 2 of the DRCR.net Protocol T study Treatment regimen: Early intensive treatment with at least five to six initial monthly doses totaling as many as eight to nine injections in year 1. For the subsequent treatment phase, fixed dosing or individualized dosing—based on VA and OCT—should/can be considered based on local context and recognizing heterogeneity and response. Intravitreal corticosteroid treatment may be considered as a first-line therapy in select cases, such as pseudophakic or post-vitrectomy eyes, or if the patient is at high risk of thromboembolic events.	Deferred focal laser (from month 6 onwards) may be considered as an adjunctive treatment. Combined laser plus steroid treatment.

India All India Ophthalmological Society Diabetic Retinopathy Task Force and Vitreoretinal Society of India consensus statement Year: 2021 [26]	anti-VEGF Treatment regimen: no specific recommendations on the choice of the treatment regimen.	If the patient has been on bevacizumab, a switch to ranibizumab or aflibercept is recommended; if on ranibizumab, a switch to aflibercept is advised. Intravitreal steroids can be considered in the following: Responding to anti-VEGFs but difficulty to maintain frequent follow-up visits; Pseudophakic patients who have reached a plateau: persistent intraretinal fluid (IRF)/VA <6/12; Persistent edema and needing cataract surgery; Occurrence of the systemic vascular event while on anti-VEGFs; Associated features such as extensive hard exudates and the presence of hyperreflective dots on OCT; Eyes post vitrectomy. Additional laser photocoagulation to treat persistent edema (considered after 4–6 injections may also be considered for the following: Persistent CSME with visible microaneurysms; If a switch to steroid is not possible (glaucoma/young phakic patient), grid +/− focal laser may be applied to areas of retinal thickening.
Australia Diabetic Macular Oedema Guidelines: An Australian Perspective Year: 2022 [22]	anti-VEGF (there is some data to suggest patients with a VA of 6/15 or worse at presentation may benefit from treatment with aflibercept) 3 loading doses of either intravitreal ranibizumab or aflibercept. Continue treatment by utilizing a treat and extend type regime. steroid implant the presence of systemic contraindications to anti-VEGF, pregnancy, children, those with learning difficulties, and recent arterial thromboembolic events such as a recent stroke or myocardial infarction.	a switch to a different anti-VEGF agent or steroids after 3–6 injections laser therapy, steroids (dexamethasone implant and triamcinolone (off-label) Australian authorities have recognized Iluvien as of 2019, but to date, this implant is not often used

"DME treatment recommendations for Asia": "for the subsequent treatment phase, fixed dosing or individualized dosing-based on VA and OCT-should/can be considered based on local context and recognizing heterogeneity and response" [21]. The recent Australian publication recommends three loading doses of aflibercept of ranibizumab and maintenance treatment by using a treat and extend regimen [22]. Steroids are usually recommended under special circumstances as the first-line treatment and as a gold standard for the second-line treatment in anti-VEGF nonresponders. There are also discrepancies regarding the laser utility, which is either not recommended or recommended only as an additional therapy [21-26].

ANTI-VEGF DIFFERENCES AND DURABILITY

With the most studied and commonly used anti-VEGFs (aflibercept, bevacizumab and ranibizumab), intensive treatment is always needed, especially in a loading faze to achieve optimal treatment outcomes. However, based on the results of the DRCR.net protocol T RCT, the choice of anti-VEGF agent depends on baseline VA, which is underlined by international guidelines [21-26]. Standard practice

would be to commence aflibercept treatment for DME, where VA is below 69 letters.

The DRCR.net protocol T was a multicenter RCT comparing aflibercept, bevacizumab and ranibizumab in DME treatment [27-29]. The mean number of injections during the period of 2 years was comparable for all three anti-VEGF treatments: 13,4 (aflibercept), 14,3 (bevacizumab) and 14,1 (ranibizumab). A total of 660 adults with centers involving DME were randomly assigned to each treatment group. From baseline to 1 year, visual acuity (VA) improved in all three groups, while aflibercept was more effective at improving VA in eyes with initial VA less than 69 ETDRS letters (mean gain of 18,9 letters, compared to ranibizumab with 14,2 letters, P = 0,003, and bevacizumab with 11,8 letters, P < 0,001) [28]. At 2 years, aflibercept was also superior in visual acuity improvement (18,1 letters from baseline) to bevacizumab (13,3 letters, P = 0,02), whereas it was equal to ranibizumab (16,1 letters, P = 0,18) in patients with worse initial VA (< 69 letters) [27]. At 5 years, 3 years after the end of the RCT, 68% of patients completed the follow-up assessment. No significant difference was observed among the three medication groups in VA change either from baseline to 5 years or from 2 years to 5 years [29]. Based on these results, one may conclude that the baseline BCVA (best corrected visual acuity) letter score determines the choice of treatment. In eyes with BCVA less than 69, treatment with aflibercept and ranibizumab should be recommended, while all three medications are comparable in patients with a BCVA letter score of 69 or more at a baseline examination.

Regardless of the favorable results of anti-VEGF treatment in DME based on RCTs, the results of the real-world data indicate a lower number of injections and worse visual outcomes. Due to the high treatment burden both for patients and health care systems associated with frequent anti-VEGF injections, real-world studies have highlighted the prevalence of undertreatment of DME patients, regardless of the world region [10, 11].

Brolucizumab (Beovue, Novartis) is a single-chain antibody fragment to VEGF. Brolucizumab was proven to achieve a significantly higher concentration (12-fold) at a dose of 6 mg than aflibercept (2 mg). This could be a possible explanation for the prolonged durability. Two phase III RCTs, the KESTREL and KITE trials, proved its safety and efficacy for treating DME; subsequently, in June 2022, brolucizumab was approved by the FDA for the treatment of DME [30]. These trials showed a comparable rate of intraocular inflammation compared to aflibercept in the DME patient population. nAMD RCTs of brolucizumab (HAWK, HARRIER) have reported increased intraocular inflammation, retinal vasculitis, and retinal artery occlusions [31]. Brolucizumab demonstrated noninferiority to aflibercept at 52 weeks and maintenance of VA gains on 12-week dosing regimens. Brolucizumab groups received 5 loading doses every 6 weeks (q6w) followed by 12 weeks (q12w) of dosing, with optional adjustment every 8 weeks (q8w) if disease activity was identified at predefined assessment visits. The percent chances for maintaining q12w dosing of 6 mg brolucizumab after the loading phase through the end point (week 52) were 55,1% in the KESTREL trial and 50,3% in the KITE trial [30]. This allows us to conclude that brolucizumab provides an additional therapeutic option with the major benefit of longer intervals between injections.

FARICIMAB

Faricimab (Vabysmo; Roche AG, Basel, Switzerland) is a bispecific antibody that targets both angiopoietin-2 (Ang-2) and VEGF-A. Both of these factors have a documented role in the pathomechanism of DME, disruption of the blood–retinal barrier (BRB) and activation of chronic, subclinical inflammation. Ang2 potentiates the action of VEGF. It has been demonstrated that VEGF-induced vascular permeability triples in the presence of Ang2 [32]. Two multiarm phase III studies, YOSEMITE and RHINE, were conducted to study the efficacy, safety and durability of faricimab (6.0 mg) delivered at a personalized treatment interval up to once every 16 weeks (q16w). Nearly 75% of patients who received faricimab had a treatment interval of q12w, and half were extended to q16w (YOSEMITE 52,8%; RHINE 51%). In terms of BCVA gain, faricimab was proven to be noninferior to aflibercept (q8w) when used in a personalized treatment interval regimen [33]. Currently, the RHONE-X extension study is exploring the long-term efficacy and safety of faricimab; the results are expected to be published in August 2023.

FLEXIBLE TREATMENT REGIMENS – TREAT AND EXTEND

A treat-and-extend regimen (TER) is an individualized dosing scheme that was developed to avoid periodic recurrences of macular edema with the use of a fixed or PRN regimen of anti-VEGF injections. It was incorporated from neovascular AMD. One key advantage of the TER regimen is a reduction in the

number of visits. Another advantage of TER is its increased efficacy based on proactive treatments. To date, few studies have explored the advantages of TER in DME patients using ranibizumab and aflibercept. Regarding ranibizumab, the RATAIN and TREX-DME trials reported significantly fewer injections and visual and anatomic gains with Ter than with the use of fixed and PRN regimens [34, 35]. Similar results were obtained for aflibercept. Curry B. *et al*. conducted a prospective, single-arm, open-label study with a study group of 36 DME patients. The authors concluded that for the majority of patients (75%), a TER regimen of aflibercept in the first 2 years of therapy is a practical alternative to PRN [36]. The (intraVItreal afliBercept In diabetic Macular edema) VIBIM study was a prospective, multicenter, single-arm, 104-week study, with 48 included patients from South Korea. The TER regimen reduced the frequency of clinic visits. The mean number of intravitreal injections decreased gradually from 8.5 in year one to 3.9 in year two. The injection interval was extended up to 12 weeks in 56.5% of patients [37]. Hirano T. *et al*. implemented a TER regimen with the longest treatment interval set to 16 weeks with an adjunct focal/grid laser in a group of 30 patients. The authors also concluded that TER may be a rational 2-year treatment strategy for DME [38]. The VIOLET trial was a randomized, Phase IIIb, 100-week, noninferiority study in patients with CI- DME who were previously treated with aflibercept for 1 year according to the European label. The main aim of the study was to compare two flexible regimens of intravitreal aflibercept (PRN and TER) with a fixed regimen (every 8 weeks). The study group included 458 patients. No clinically relevant differences were observed between the groups for the changes in BCVA letter score, as well as changes in CFT at Week 52 and Week 100. The mean number of intravitreal injections was 12,3 in the fixed regimen, 11,5 in PRN and 10,0 in TER, while the mean number of visits was 16,1, 25,0 and 13,3, respectively [39].

All these data prove that flexible management of patients with DME reduces the treatment burden associated with anti-VEGF therapy while maintaining functional and anatomical improvement and further stability.

HIGH-DOSE AFLIBERCEPT

Currently, an interesting concept of high-dose aflibercept is being studied extensively in the phase III PHOTON trial. The trial is designed to investigate the safety and clinical efficacy of a high dose (8 mg) of aflibercept (Regeneron Pharmaceuticals, Inc.) relative to 2 mg aflibercept in DME. The patients were randomized to three groups: 5 injections of 2 mg aflibercept monthly followed by every 8 weeks; 8 mg of aflibercept every 12 weeks after 3 monthly loading doses; or 8 mg of aflibercept every 16 weeks after 3 monthly loading doses [40]. Promising, preliminary one-year results were presented during the American Academy of Ophthalmology. Eight mg aflibercept demonstrated noninferiority in vision gains in both the q12w and q16w dosing regimens after the loading phase at 48 weeks compared to a 2-mg aflibercept q8w dosing regimen. Moreover, 91% of q12w and 89% of q16w patients maintained those intervals at 48 weeks. The safety profile of 8 mg aflibercept was similar to that of 2 mg aflibercept in both trials [41].

STEROID IMPLANTS (DEXAMETHASONE OR FLUOCINOLONE IMPLANTS)

The rationale for steroid use in DME is that low-grade, subclinical inflammation markedly contributes to the development and worsening of DR and DME. Subclinical inflammation along with adherent leukocytes are responsible in the process of vascular pathologies. Leukostasis in retinal capillaries occurs early in DME development, which further leads to BRB dysfunction [31, 42]. Corticosteroids provide anti-inflammatory and anti-edematous effects by targeting three separate pathways: reducing the activation of proinflammatory mediators (IL-6, IL-8, TNF, VEGF, MCP-1, and ICAM-1), blocking the arachidonic acid pathway and preventing changes in retinal glia (Müller cells) [31, 42].

Dexamethasone intravitreal implant (DEX implant, Ozurdex; Abbvie) is a sustained-release biodegradable implant containing 700 μg dexamethasone, which was approved for DME treatment by the U.S. FDA in 2014. The efficacy of dexamethasone implants was primarily confirmed in RCTs (MEAD, CHAMPLAIN) [43, 44]. The MEAD study group reported the results of two randomized, multicenter, masked, sham-controlled, phase III clinical trials with identical protocols. A total of 1048 patients with DME were randomized to the 0.7 mg or 0.35 mg DEX group or sham group. Over 20% of patients achieved ≥15 letter gain in the study group. The main conclusion was that dexamethasone implants 0.7 mg and 0.35 mg met the primary efficacy endpoint, which was BCVA improvement. The safety profile was adequate, and the two most common adverse events were cataract formation and intraocular pressure (IOP) rise [44]. The CHAMPLAIN trial was a multicenter, prospective study in eyes with refractory DME and a

history of pars plana vitrectomy (PPV) with a 26-week observation time. A total of 30.4% of patients gained a significant improvement in BCVA, ≥10 letters at 8 weeks [43]. In clinical practice, Oxurdex retreatment is recommended after approximately 6 months if there is decreased vision and/or an increase in retinal thickness subsequent to recurrent or worsening DME.

Fluocinolone acetonide (FAc, Iluvien; Alimera Sciences, Inc., Alpharetta, GA, USA) containing a dose of 0,19 mg was approved by the FDA in 2014 in patients who did not show a significant elevation of IOP while treated with corticosteroids. The pharmacokinetic FAMOUS study proved that FAc provides continuous delivery in the vitreous bode for at least one year. The FAME studies were two prospective, parallel, randomized, phase III, multicenter clinical trials. DME patients (956 in total) were included in three groups: 0,2 or 0,5 μg fluocinolone acetonide or sham injection. Twenty-eight percent of patients in each of the fluocinolone groups gained ≥ 15 letters of BCVA at 24 months. The rate of cataract extraction of phakic eyes was significantly higher with an implant (74,9%) versus 23,1% for sham. The rates of incisional glaucoma surgery were 3,7% in the study group and 0,5% in the sham group at 2 years.

Real-world data have supported the promising findings of initial RCTs. Bush *et al*. conducted a multicenter study (110 eyes from 105 patients; anti-VEGF group: 72 eyes, DEX group: 38 eyes) and concluded that in a real-world setting, eyes with refractory DME switched to DEX implant had significantly better visual and anatomical outcomes at 12 months than those that continued treatment with anti-VEGF therapy [45]. Additionally, a meta-analysis evaluating the effects of Oxurdex treatment in DME refractory to anti-VEGF including 3859 patients from 15 studies revealed a significant vision gain at a mean follow-up period of 6 months. The mean difference in BCVA was a gain of four lines or 20 ETDRS letters [46]. Kodjikian L. *et al*. reviewed 32 studies (38 treatment groups; 6842 eyes) evaluating the efficacy of anti-VEGF and 31 studies (35 treatment groups; 1703 eyes) evaluating the efficacy of DEX implants over a period of 10 years (2005-2016). The authors concluded that studies investigating DEX implants report significantly better visual gains in real-life practice. This revealed difference could be because Dex-implant is administered once at 6 months, and the patient's treatment burden is lower compared to anti-VEGF treatment, namely, suboptimal patient compliance can disrupt the monthly or bimonthly dosing schedule required for optimal results in anti-VEGF therapy [47]. Long-term real-world studies, such as the RESPOND and Retro-IDEAL studies, confirm that FAc implants provide clinically significant improvements in VA and macular thickness up to a 3-year follow-up [48, 49].

Referring to international guidelines, steroid implants should generally be considered in nonresponders who have already been treated with a loading dose of 3-6 anti-VEGF injections [21–25]. However, authors originating from the Indian Ophthalmological Society recommend switching to another anti-VEGF agent after 2–3 injections and to steroids after 6 ineffective injections [26]. Additionally, under special circumstances, steroid treatment is recommended as the first-line therapy in special patient groups: children, patients with learning difficulties, pregnant women, patients with systemic contraindications to anti-VEGF (recent thromboembolic events) [22], pseudophakic or post vitrectomy eyes [21], patients with a history of a significant cardiovascular event, and those who are not able to come for intravitreal injections monthly in the loading phase of therapy (first 6 months) [25].

Moreover, studies have shown that there is a subgroup of DME patients characterized by low or normal VEGF intravitreal levels and higher concentrations of inflammatory markers who do not effectively respond to first-line anti-VEGF treatment. Chronic DME may also show a limited response to anti-VEGF drugs. Several OCT biomarkers have been identified and described to predict favorable responsiveness to antiangiogenetic or anti-inflammatory treatment. These biomarkers, namely, the presence of multiple retinal and choroidal hyperreflective foci (HRF), disruption of the outer retinal layers (DRIL), large, intraretinal cysts extending into the outer retina, and chronic subretinal fluid (SRF), suggest that steroids may be a drug of choice over antiangiogenetic agents. In the future, such patients may be good candidates for an early switch to steroid therapy [50].

Major benefits arising from steroid implant use include less frequent injection, and continuous dosing also ensures that treatment is maintained steadily even in cases of suboptimal patient compliance. The functional effectiveness in gaining visual acuity is retained in cases of chronic DME refractive to anti-VEGF treatment. Anti-VEGF therapy is regarded to be highly effective as the first-line treatment in the early phase of DME, but steroids become more effective in

cases of chronic DME. Clinicians need to be aware that treatment should be switched to steroid therapy once patients are not responding to anti-VEGF therapy. Clinicians must be familiar with potential complications, including high-rate cataract formation and IOP rise, which could lead to irreversible glaucomatous optic neuropathy.

SURGICAL TREATMENT

Pars plana vitrectomy (PPV) has been considered a potential treatment option for DME. Surgery is the treatment of choice in the presence of anterior-posterior traction coexisting with DME. Tangential traction may be considered an indication for surgery. There is no consensus regarding the utility of PPV in the absence of vitreoretinal traction [25].

A series of studies have shown favorable results of vitrectomy on DME with vitreomacular traction, including a prospective cohort study conducted by DRCR.net. The study group included 87 eyes with DME. OCT showed central subfield thickness >300 microns and coexisting vitreomacular traction. Patients were treated with PPV. At 6 months, retinal thickness was reduced in most eyes, with median CST decreased by 160 microns. Visual acuity improved by ≥10 letters in 38% and deteriorated by ≥ 10 letters in 22% [51].

Previous studies have not statistically confirmed the usefulness of vitrectomy in the treatment of DME without coexisting traction. It has also been emphasized that the morphological improvement after surgery is not correlated with the functional BCVA gain. Moreover, PPV interferes with the potential pharmacokinetics of intravitreal drugs. The role of surgery in refractory DME without coexisting tractions has yet to be established [52, 53].

COMBINATION THERAPY

Combining different approaches at the same time is less frequently reported in the literature and less frequently recommended. This is mostly due to the lack of conclusive scientific evidence. Nevertheless, the combination of pharmacological treatment with laser photocoagulation (focal or macular grid) may be considered.

However, it is worth being aware that combined therapy was also common in studies that are not associated with it. In the Protocol T extension phase (after 24 months, up to year 5 of the study), various drug combinations were allowed, and approximately 10% of patients received steroids, 10% peripheral laser, and 10% macular laser, with median anti-VEGF administrations approaching zero [27, 29].

The authors of the recent Cochrane systematic review concluded that a combination intravitreal treatment with anti-VEGF and steroids was not superior to monotherapy. Additionally, there is evidence for this statement of low-certainty [54]. Further investigations are necessary to provide sufficient, convincing conclusions.

SUMMARY

The current approach to DME treatment includes frequent monthly or bimonthly intravitreal anti-VEGF injections. This regimen continues to be the gold standard treatment for DME. However, not all patients respond equally to this therapy due to several reasons, such as refractory DME, high treatment burden and coexisting morbidities. Therefore, real-world data results may differ from those of RCTs in terms of vision gain and anatomical improvement. The current proposed solutions include the implementation of new therapeutic agents, high dosing of already established drugs, new treatment regimens, such as treatment and extension, and early switching to less frequent steroid dosing. Further studies need to be conducted to solve this growing problem in the future to decrease the treatment burden for patients as well as for health systems.

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