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Management of Diabetic Macular Edema in Current Clinical Practice: A Review

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Abstract

Diabetes is the most common cause of blindness in working age adults in developed countries. The last decade has seen major advances in the management of diabetic macular edema (DME), with the emergence of numerous therapeutic alternatives whose role is not yet fully defined. In this context, we present an updated review and guide to the clinical management of DME. In this review we discuss the role of complementary studies suggesting different courses of action based on the clinical, angiographic and tomographic classification of DME, and we highlight the role of laser therapy in the treatment of focal and multifocal macular edema. In cases of resistant or diffuse DME with central involvement, we propose the combined use of antiangiogenic drugs or intravitreal corticosteroids followed by laser. In patients with DME with a tractional component and functional repercussion, a surgical approach may be indicated.

Keywords: Diabetic macular edema; Photocoagulation; Vitrectomy; Intravitreal antiangiogenic drugs; Intravitreal corticosteroids

Abbreviations: DME: Diabetic Macular Edema; PDR: Proliferative Diabetic Retinopathy; anti-VEGF: anti-Vascular Endothelial Growth Factor; IVB: Intravitreal Bevacizumab; IVR: Intravitreal Ranibizumab; ETDRS: Early Treatment Diabetic Retinopathy Study; DRCR.net: Diabetic Retinopathy Clinical Research Network; CSME: Clinically Significant Macular Edema; HbA1C: Glycosylated Hemoglobin; OCT: Optic Coherence Tomography; FA: Fluorescein Angiography; TDME: Tractional Diabetic Macular Edema; IT: Intravitreal Triamcinolone; BCVA: Best Corrected Visual Acuity; IOP: Intraocular Pressure; PPV: Pars Plana Vitrectomy; FDA: Food and Drug Administration; EMA: European Medicines Agency; ILM: Internal Limiting Membrane; FAZ: Foveal Avascular Zone; AMD: Age-related Macular Degeneration; ARVO: Association for Research in Vision and Ophthalmology; CME: Cystoid Macular Edema

Introduction

We are currently facing a world-wide "diabetes epidemic", with the number of diabetics expected to reach 300 million in 2025 [1]. Among other factors, this is due to population growth, aging, obesity and a sedentary lifestyle [2]. Approximately 25% of people with diabetes mellitus have some degree of diabetic retinopathy (DR) and 2-10% has diabetic macular edema (DME) [3]. The incidence of both conditions increases with the duration of diabetes so that after 15 years duration 15% of diabetics have DME and after 20 years more than 90% showed some degree of DR [4]. Diabetes Mellitus is considered the most common cause of blindness in the working population in industrialized countries, with DME being the most common cause of decreased visual acuity in diabetics while proliferative diabetic retinopathy (PDR) is responsible for the most severe visual deficits [1]. Laser photocoagulation has been and remains the main treatment for ocular complications of diabetes. Panretinal photocoagulation serves to avoid progression to blindness in a significant proportion of patients. However, the results of laser therapy for DME are much more disappointing, with failure to prevent progression in 50% of patients. The search for alternatives has become a priority and although the pathogenic mechanisms implicated in this process are not yet well known, the involvement of vascular endothelial growth factor has opened a new avenue of research. Numerous publications describe the usefulness of intravitreal steroids and antivascular endothelial growth factor (anti-VEGF) in the management of DME and several clinical trials in Europe and U.S.A are currently assessing safety and effectiveness. Anti-VEGF drugs are administered intravitreally and repeatedly; in a chronic disease like diabetes this is a major drawback, hence, in parallel, investigators are evaluating the possibility of combining anti-VEGF with laser treatment to improve results.

In this situation of change and uncertainty it is necessary to establish uniform criteria, based on an extensive review of the literature, as guidance in dealing with this complication, pending the conclusion of these studies and until we have new guidelines on treatment to improve the prognosis of these patients. The purpose of this review of DME management is, therefore, to present general guidelines for treatment at a time when alternative therapies are emerging. We used the classification of DME proposed by the Early Treatment Diabetic Retinopathy Study (ETDRS) [5] and treatment options reviewed refer to clinically significant macular edema (CSME). As complementary tests, the results of optical coherence tomography (OCT) and fluorescein angiography (FA) are critical for therapeutic decision-making.

Assessment Prior to Therapeutic Action

Good systemic control (blood glucose, hypertension, dislipemia, etc., is essential in diabetic retinopathy, and this is especially true in

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DME. The approach should be multidisciplinary, involving other specialists in endocrinology, internal medicine and nephrology in order to regulate glycosylated hemoglobin levels (HbA1C), blood pressure, body weight and lipid levels, which are particularly important factors. Poor metabolic control may, in some cases, justify postponing the treatment of macular edema until HbA1C levels improve, preferably below 7% [6]. Assessment of edema should always include: best corrected visual acuity, biomicroscopic fundus examination, retinography and optical coherence tomography (OCT). The use of fluorescein angiography (FA) is debatable in cases of circinate retinopathy where the source of leakage is clear. However, it is a very useful test to study perifoveal vascular network status. DME is classified into focal, diffuse or mixed, depending on the leakage pattern seen on the fluorescein angiogram [7].

Tractional diabetic macular edema (TDME) is characterized by macular thickening on OCT with loss of foveal depression and edema of the outer retinal layers. On OCT, the posterior hyaloid is thick and hyper-reflective, tense and partially detached from the posterior pole, but remains adhered to the optic disc and the highest point of the elevated macular surface. The thickened and tense posterior hyaloid exerts tangential vitreomacular traction that induces or exacerbates DME.

Biomicroscopy, unlike OCT, is insufficiently precise to determine the status of the posterior hyaloid when it is only slightly detached from the macular surface. OCT is therefore more sensitive than biomicroscopy in identifying vitreomacular adhesion and allows for earlier diagnosis of a partially detached posterior vitreous [8]. It also allows accurate and highly reproducible assessment of macular thickening.

Treatment Options

Before describing the therapeutic approach to DME, we should point out that the American Diabetic Retinopathy Clinical Research Network (DRCR.net) has suggested a reconsideration of the terms focal and diffuse macular edema. The reason lies in the fact that exploratory findings (obtained with fundus biomicroscopy and fluorescein angiography, etc.) are too inaccurate and inconsistent to support decision-making on the photocoagulation technique to be used [9]. The DRCR Network argues that it would be more constructive to use more objective terms to describe edema, such as the extent and location of the thickening, or the degree of involvement of the center of the macula, a criterion which has been used in numerous clinical trials [10-16]. However, since the classification of DME as focal or diffuse is still used in clinical practice and in recent clinical trials [17], it will be maintained throughout this review, but we will also refer to central macula involvement or not (also used in many on-going clinical trials [18-20]).

Clinically Significant Macular Edema (CSME): Focal or Multifocal

Laser treatment plays a key role in controlling this type of edema, especially when there is no central macular involvement, and provides good long-term results. The DRCR network has shown that focal laser treatment was not only safe but also more effective than intravitreal triamcinolone acetonide (IVTA) after two years [21] (Figures 2 and 3). Thus, 51% of patients in the laser arm had improved at least 5 letters in 2 years. A review of ETDRS data found that while only 10% of subjects improved with focal laser, 40% with visual acuity less than 20/40 had gained 6 or more letters in 3 years [22-25] (Figure 1).

When indicated, laser treatment is directed at micro-aneurysms situated in the center of circinate crowns, between 500 and 3,000 microns from the center of the FAZ, with spots of 50 microns only powerful enough to mildly whiten them. The adverse effects of laser

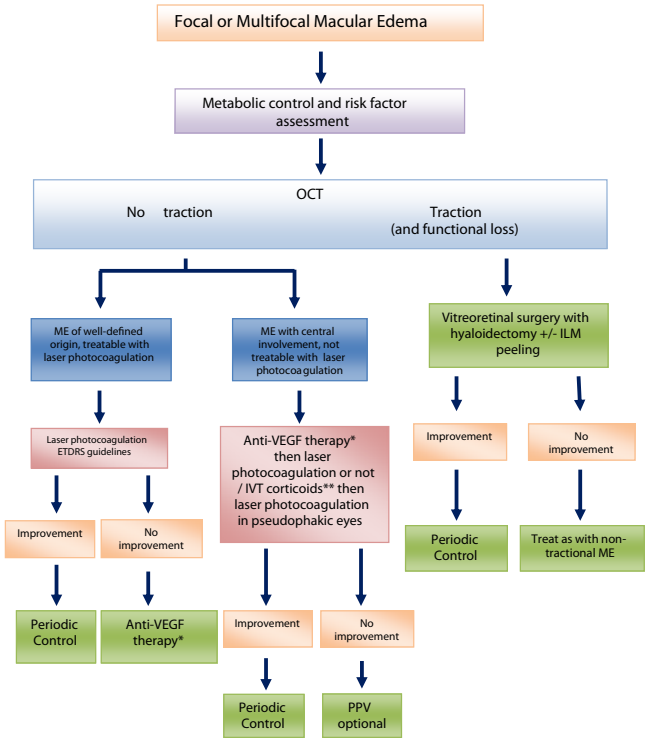


Figure 1: Treatment algorithm for focal and multifocal macular edema.

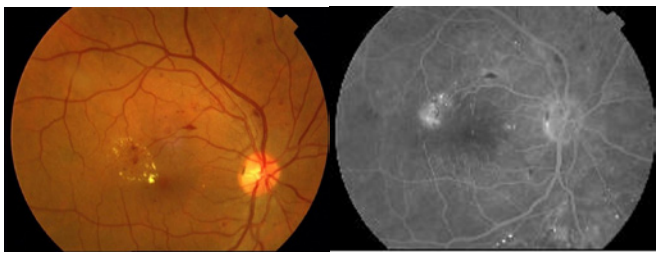


Figure 2: Angiography and retinography of focal CSME.

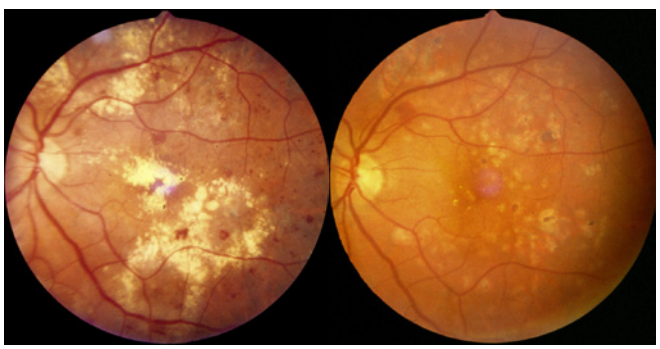


Figure 3: Multifocal CSME before and after laser treatment.

photocoagulation include loss of contrast sensitivity, burning of healthy retinal tissue [26] and the destruction of photoreceptors [27]. The latest generation of selective laser techniques such as Pascal® (Pattern Scanning Laser) [28-31] and sub-threshold micropulse diode laser offer more precise photocoagulation with less retinal tissue damage. In cases where there is clear central involvement with an impact on visual acuity and in which the lesions, are not amenable to laser treatment because of proximity to the fovea, antiangiogenic therapy is a good alternative, as shown in a recent study carried out by the DRCR.net using ranibizumab [19]. Antiangiogenic therapy may also be effective in mixed type edema where laser therapy is hindered by the central macular thickening (usually with values greater than 400µm on OCT) [32]. In these cases the options available are: antiangiogenic therapy followed by laser or not [33], intravitreal steroid therapy followed by laser [34-37] in pseudophakic patients [18] (IVTA alone does not show better results than long-term laser). The most widely used option is intravitreal triamcinolone, 4 mg in non-vitrectomized eyes and 8 mg in vitrectomized eyes. However, the optimal dose has yet to be established. This is discussed more fully in the following section on diffuse CSME.

In cases of vitreous-macular traction with functional repercussion, pars plana vitrectomy (PPV) [38-40] with or without peeling of the internal limiting membrane (ILM) [41-43] and / or IVTA / anti-VEGF [34-37] should be considered. However, the role of surgery in the management of DME remains unclear since the potential benefits versus the risks of surgery have not been established in the context of a long-term randomized clinical trial [44].

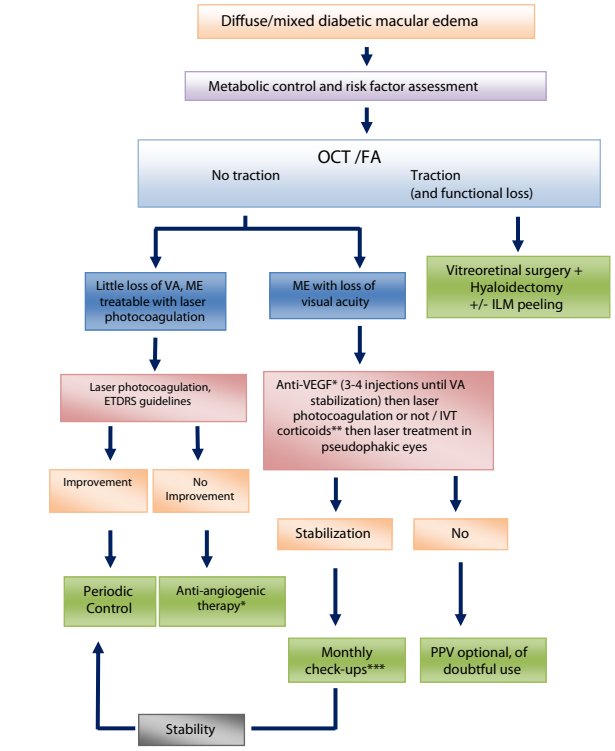
Diffuse CSME

When there is diffuse CSME with vitreoretinal traction, the most widely accepted therapeutic indication is PPV with hyaloidectomy [39,40,45,46] (Figure 4). There is ongoing debate about ILM peeling [47-52] and the use of antiangiogenic or intravitreal corticosteroids at the end of surgery [53-54] (Figures 5, 6 and 7).

If there is no traction, the approach to date has been the application of modified grid laser. This involves smaller (50µm) and less severe burns (light gray). Microaneurysms are treated directly but without attempting to achieve color change. Laser is also applied to areas of retinal thickening and areas of non-perfusion induced by the edema. According to ETDRS criteria, laser treatment must be repeated after 3-4 months if the edema remains unresolved (up to 4 treatments). However, the results obtained with this technique applied to diffuse edema are less satisfactory than for focal macular edema and often disappointing, only avoiding moderate loss of visual acuity in 50% of patients, while 26% continue to lose vision over the long term and only 3% experience slight improvement of visual acuity. This has led to constant research into new therapeutic alternatives in recent years, based on a better understanding of the pathogenesis [55].

Intravitreal corticosteroids followed by laser in pseudophakic eyes and anti-angiogenic drugs with or without laser are currently the most promising options, but it takes at least 3 years of follow up with these new therapies to reach definitive conclusions.

However, there is already enough scientific evidence to say that the paradigm of DME treatment is changing. Many studies support the use of antiangiogenic drugs in this type of edema, especially when there is central involvement [33,70,76,77,99,100]. In fact the European Medicines Agency (EMA) has approved the indication of ranibizumab and pegaptanib for DME. The variable that governs treatment with ranibizumab is visual acuity, more than central macular thickness



*The only drug currently approved for this indication is Ranibizuamb. Pegaptanib and Bevacizumab are used off-label
**Corticoids are used off-label. This applies to both intravenous triamcinolone and implantable slow-release devices
***Assuming patient attendance is possible

Figure 4: Treatment algorithm for diffuse and mixed macular edema.

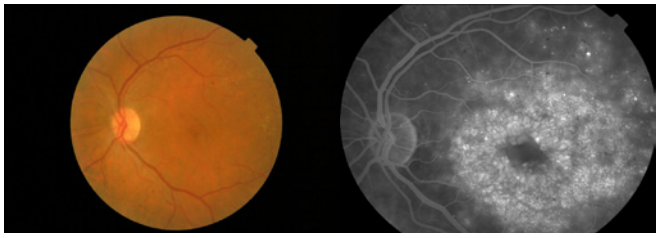


Figure 5: Retinography and angiography of diffuse CSME.

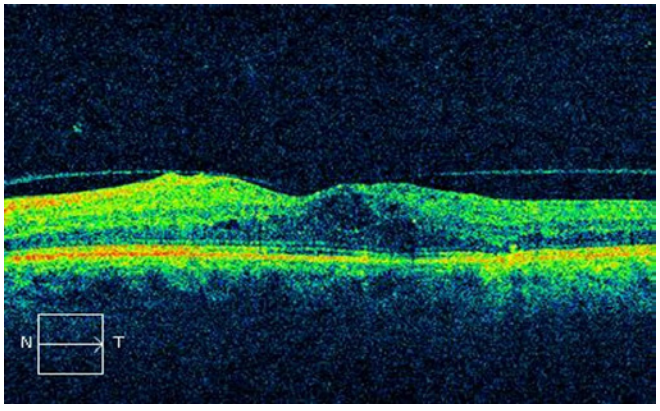


Figure 6: OCT of a macular edema with vitreo-macular traction.

or the type of edema involved. It is left to the ophthalmologist to decide whether to use ranibizumab alone or in combination with laser therapy. The recommended treatment plan for ranibizumab, in combination with laser or not, requires the completion of a minimum of 3 or 4 consecutive intravitreal injections administered on a monthly basis until visual acuity ceases to improve. Improvement is considered a visual gain of 5 letters and retinal thickness reduction of 10% from one visit to the next, and the absence of changes in visual acuity in the last three visits is considered as stable. When stability is achieved, treatment should be discontinued. Subsequently, the patient should be seen every 2-3 months. If visual acuity declines due to progression of edema (increased central macular thickening), treatment should be re-initiated, this time with intravitreal injections as needed to reach stability again. Research is still ongoing and very long periods of follow-up are needed to define appropriate treatment guidelines.

Ocular complications appear to be more related to the injection procedure than to the anti-VEGF itself. These include endophthalmitis (≤ 0.8% [17-19]), lens injury (0 - 0.7%) [56-57] or retinal detachment (0.03% -0.17%) [52-54,58]. The systemic safety profile is good and similar to that reported in age-related macular degeneration (AMD) [25].

Another aspect that must also be considered is cost- effectiveness of treatment, due to the high price of some of these drugs [59]. What does seem clear is that the use of laser therapy in combination with anti-VEGF treatment significantly reduces the number of annual anti-VEGF injections needed to treat DME. The following section outlines the situation regarding new drug therapies available at present.

Intravitreal steroids

The use of intravitreal corticosteroids in DME is an off-label procedure because, to date, triamcinolone acetonide, dexamethasone and fluocinolone in controlled release implants are considered investigational new drugs. It is therefore necessary to obtain consent from the patient for off-label use. At present there are three preparations:

Triamcinolone acetonide: Intravitreal injection of 1 or 4 mg of triamcinolone alone fails to improve the functional outcome of laser photocoagulation in the long term (3 years) in patients with active DME, with the added disadvantage that it is associated with a significantly higher rate of adverse effects, primarily cataracts and glaucoma. In contrast, BCVA results slightly favored laser over IVTA (the laser group gained an average of 5 letters while in IVTA groups this gain was 0) [60].

The combination of IVTA (4 mg) and early laser therapy (3-10 days after injection) has only proven effective in pseudophakic eyes [18,19]. Thus, in patients with central macular edema that are pseudophakic, IVTA followed by laser therapy was more effective than laser alone (at two years of follow up) but increased the risk of elevated intraocular pressure. The complications associated with the use of IVTA [61-64] (glaucoma, retinal detachment, cataract, endophthalmitis) and legal issues that may arise from off-label use have made us more restrictive in terms of patient selection. However, in diffuse CSME with considerable central macular thickening (Figure 8), its efficiency makes it the most commonly recommended drug. The dosages commonly used are 1, 2 or 4 mg IVTA in non-vitrectomized eyes while 8 mg doses are recommended in vitrectomized eyes [65]. In cases where the central macular thickening is not so marked, we would recommend anti-angiogenic drugs whose side effects seem less pronounced. Since the effect of IVTA is transient [66-69], another possible approach is to initiate treatment with IVTA and continue with an antiangiogenic and / or laser therapy [70].

Other alternatives such as dexamethasone or fluocinolone implants are currently being evaluated. Preliminary studies [71,72,74] show significantly fewer side effects than those described for IVTA. They could therefore become a valid therapeutic option in selected cases of macular edema (>400 microns, treatment resistant). They also allow the possibility of periodic re-treatment but at greater intervals than those required for anti-VEGF.

Ozurdex (Allergan, Inc, Irvine, CA, USA): This is a biodegradable implant that releases dexamethasone during 4 to 6 months. The results of a phase II clinical trial are already published [71] and phase III is under way. For all efficacy parameters, the response to treatment with doses of 700 μg (0.7mg) is greater than with 350 μg, suggesting a dose-response relationship. According to these results, doses of 700 μg, achieved an improvement of more than 10 EDTRS letters in just over 30% of patients and more than 15 letters in about 20% at 6 months of treatment, with an acceptable safety profile. No differences between the treatment group (receiving 700 or 350 μg) and controls (no treatment) were observed regarding cataracts or progression at six months. No cases of retinal detachment or endophthalmitis were observed in the treatment group; 7.5-16.4% showed increased intraocular pressure (IOP), mostly in the first week after intravitreal injection. All responded to medical treatment and neither laser therapy nor surgery were required to control the IOP [71]. About 20% of patients experienced

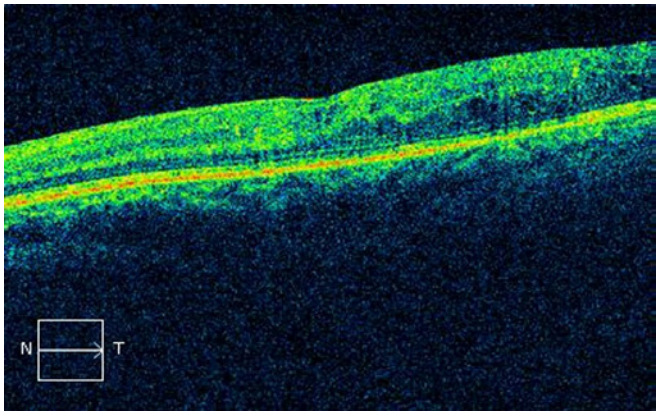


Figure 7: OCT of the same patient after vitreo-retinal surgery.

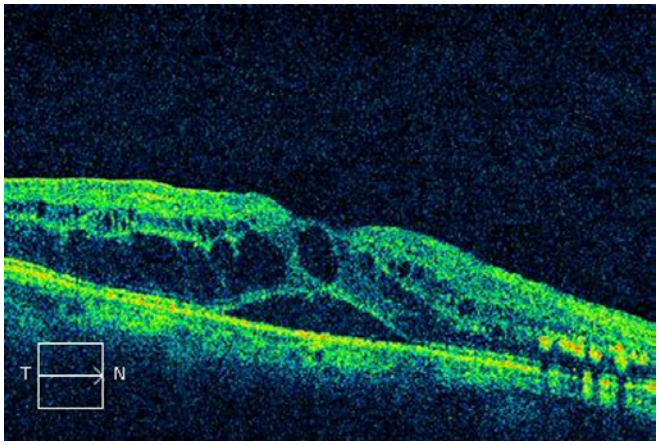


Figure 8: OCT of a patient with large mixed CSME and central macular thickening.

slight vitreous hemorrhage and a slightly higher percentage had some degree of cellularity or anterior chamber flare as a result of the needle insertion procedure, but these problems can be reduced by improving the insertion technique [72]. Significant improvement in visual acuity was observed in the treatment group at two and three months, but at 6 months there were no significant differences with respect to the controls. The optimum interval before re-treatment remains to be established. Of particular interest is the apparent usefulness of this implant for the control of DME in vitrectomized eyes [73]. It is known that vitrectomized eyes show altered pharmacokinetics and that clearance is much faster, thus limiting the effectiveness of many treatments. However, with 0.7 mg of dexamethasone, therapeutic levels of the drug were maintained during 6 months and efficacy was acceptable in these patients (at the end of the study 21.4% had gained at least 10 letters and 42.9% at least 5 letters). The average gain at 2 months was 6 letters and at 6 months 3 letters. The safety profile was similar to that of patients with non-vitrectomized eyes.

Iluvien (Alimera Sciences, Alpharetta, GA): This is a fluocinolone acetonide intravitreal insert by Alimera Sciences, Inc. The FDA is currently considering approval of Iluvien, a non-biodegradable device, for the treatment of DME on the basis of the publication of the FAME study results [66]. This was a phase III, multicenter, prospective, controlled clinical trial which included 956 patients with DME treated with this device and followed for 3 years. Rescue laser treatment was possible after 6 weeks and retreatment after 12 months. Preliminary results [74], suggest that the most beneficial dose is 0.2 µg / day fluocinolone acetonide (compared to 0.5 µg / day). Iluvien had a beneficial effect on visual acuity as from 3 weeks of implantation in the vitreous cavity and this was maintained throughout the study, with 29% of patients gaining more than 15 letters compared with 18% in the control group who received sham injections. At two years, mean improvement in visual acuity was 4.4 letters. With respect to safety, the most frequently observed adverse effects were cataracts (74.9% versus 23.1% in the control group), but patients requiring cataract surgery during the study showed as much improvement as those who had undergone surgery for cataracts before being included in the trial. Intraocular hypertension was not uncommon (18%) and 4% required surgical treatment. The incidence of serious cardiovascular events was similar between the two groups.

Vascular endothelial growth factor inhibitors

Pegaptanib sodium injection (Macugen®; Eyetech Pharmaceuticals / Pfizer, Inc, New York, NY): The Macugen Diabetic Retinopathy Study Group (Berlin, WOC 2010) reported that pegaptanib administered at a dose of 0.3 mg every 6 weeks resulted in significant improvement in visual acuity, decreased central macular thickness and reduced the need for laser treatment in patients with DME. Mean improvement in visual acuity obtained with this regimen was 4.7 letters at week 36 (9 months, after 6 injections of pegaptanib), with a gain of more than 10 letters in 37% of patients versus 20% in the control group at week 54 (1 year, 9 injections) and a safety profile similar to that observed in patients with AMD. The optimum combination of pegaptanib and focal laser has yet to be established [25].

Bevacizumab (Avastin®, Genentech Inc., San Francisco, CA): In a prospective randomized trial of intravitreal bevacizumab (IVB) versus laser therapy for the management of diabetic macular edema, IVB administered at a dose of 1.25 mg every 6 weeks, with a loading dose of 3 injections and then as needed, achieved better functional outcomes than gold standard treatment (laser therapy using ETDRS guidelines: a minimum of 1 to a maximum of 4 modified grids) at 12 months. In the IVB group, 31% of patients gaining more than 10 letters after one year versus 7.9% in the control group, and the safety profile of IVB was good [20]. At 12 months, after an average 9 injections of IVB, the treatment group showed a gain of 8 ETDRS letters versus a loss of 0.5 letters in the laser group with an average of 3 modified grids. IVB has beneficial effects on both visual acuity and short-term central macular thickness in DME [20,33,75-77]. Many small studies suggest that IVB is more effective in naïve patients than in those with DME refractory to other treatments [78].

Ranibizumab (Lucentis; Genentech, South San Francisco, CA): Intravitreal ranibizumab (IVR) at a dose of 0.5 mg (allowing retreatments), as monotherapy or associated with laser, improves the results of laser alone in CSME with a rate of adverse effects similar to that observed in patients with AMD [9]. Effectiveness is maintained during 24 months as shown by DRCR.net and READ-2 studies [79]. As already noted, the combination of IVR and laser therapy significantly reduces the amount of residual edema and the number of injections necessary to maintain the effect, which may also significantly reduce the risk of adverse effects and the cost of treatment. Thus, the mean number of injections needed in the ranibizumab group (IVR) on monotherapy was 9.3 over 24 months versus 4.9 in the combined-therapy group IVR + laser over the same period [79]. There was little difference in terms of BCVA: improvement was 7.7 letters in the monotherapy group compared to 6.8 letters in the combined therapy group. Also, the combined therapy group showed reduced amount of residual edema (at month 24, the mean central thickness was 340 µm in the IVR monotherapy group vs. 258 µm in the combined IVR + laser therapy group). Currently, and based primarily on the results of the RESTORE [17], RESOLVE [80] and READ 2 [79] studies, the European Medicines Agency (EMA) has approved the indication of ranibizumab for the treatment of diabetic macular edema. In contrast pegaptanib has not yet been approved for DME and bevacizumab is not being considered, and still require permission for off-label use, whether used in isolation or in combination with laser therapy. If the use of one of these therapies does not result in improvement, further treatment options are very limited and PPV can only be used in selected cases [81,82] as various studies have found no improvement [83,84].

Cystoid Macular Edema

Although this is a diffuse type of DME, its description may be useful because it presents singular therapeutic and prognostic aspects. When central cysts appear on OCT, the general tendency is to use anti-VEGF / steroids followed by laser therapy rather than the latter alone. CME presents unique prognostic factors, since the existence of cysts may be due to necrosis of Müller cells with accumulation of fluid in the extracellular space [85], and they are associated with worse visual acuity [86]. In patients with CME without evidence of traction, the choice is the use of intravitreal corticosteroids and / or anti-VEGF followed, optionally, by modified grid laser therapy [87-89]. The optimum corticosteroid dose is not yet fully established [90], and furthermore, some studies have found no long-term advantages compared to laser alone [91,92]. However, CME may be a promising candidate for combination therapies [93]. When improved visual acuity is recorded, it may only be a transient effect [94], so further injections may be needed, followed by laser therapy or not. If there is no improvement, PPV may be considered since it seems to slightly improve and stabilize visual acuity [95]. In cases of CME with vitreomacular traction, PPV is recommended, without ILM peeling in those cases where evolution time is unknown or exceeds 6 months (due to the risk of inducing a

macular hole). In cases of CME with less than 6 months evolution, ILM peeling may be performed if the morphology of the cyst on OCT suggests that this maneuver is beneficial; in these patients, PPV is more effective than in those without traction and / or more than 6 months of evolution [39] (Figure 9).

Ischemic Macular Edema

Macular ischemia is defined by clinical signs such as:

- Increased foveal avascular zone (FAZ) ≥ 1000 μ.
- Rupture of the perifoveolar ring on the edge of the FAZ.
- Area of non-perfusion within one disk diameter of the center of the fovea.

In predominantly ischemic DME with traction, PPV is a definite possibility, but if there is no traction, the prognosis is also poor. Eyes with macular ischemia do not show significant improvement with the use of IVTA [96]. In addition, the use of non-selective anti-VEGF is initially contraindicated because VA shows no improvement and may actually decrease at three months of follow up. Even though the edema may decrease, this does not correlate with improvements in visual acuity; thus in one study, 50% of patients lost at least one line of vision (ETDRS) and 22% lost at least 3 lines, and only 16.7% improved at least 1 line [97].

However, in a subsequent non-randomized study in which at least one IVB injection was administered in 10 eyes with DME associated with significant macular ischemia, the authors observed anatomical and functional improvement (improvement of both visual acuity and decreased central macular thickness) without increasing the ZAF after one year of follow-up [98]. Other authors have also found no exacerbation of macular ischemia with the use of repeated injections of bevacizumab after 12 months follow-up [99].

Diabetic Macular Edema with Massive Lipid Deposits

In some patients with chronic macular edema, lipid deposits concentrated in the macular area irreversibly damage the photoreceptors, thereby rendering any kind of treatment ineffective.

In fact, laser treatment of this type of CSME with abundant and confluent hard exudates has been associated with an increased incidence of subretinal fibrosis and atrophy of the retinal pigment epithelium (RPE). In these cases, before the VA is affected, tight control of dyslipidemia (total and LDL cholesterol) can result in better results in terms of preserving visual function and macular anatomy [100].

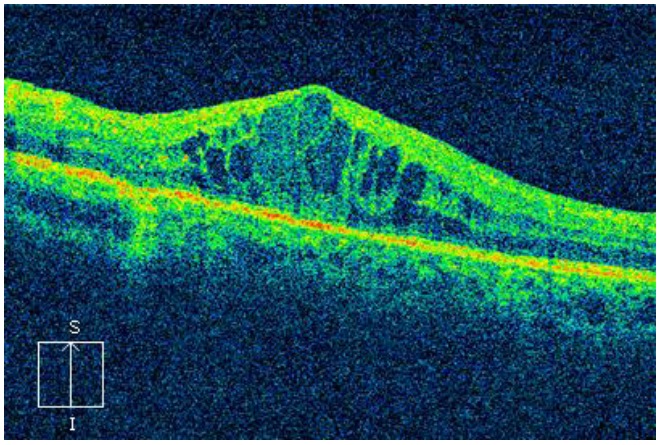


Figure 9: Non-tractional cystoid macular edema.

Conclusions

Laser photocoagulation, alone or associated with new drugs, continues to play a relevant role in the treatment of diabetic macular edema. EMA-approved intravitreal ranibizumab has shown its utility, administered alone or in combination with laser photocoagulation. At present, other anti-VEGF and intravitreal corticosteoids that show promising results are used off-label and await official approval for this indication.

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