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Diabetic macular edema: a literature review

Wellington Fernando Risso[1], Matheus Roque Pinheiro[1], Leonardo Amarante Pereira[1], Júlio Zaki Abucham-Neto[1], Glaucia Luciano da Veiga[1,2], Fernando Luiz Affonso Fonseca[1,2,3], Vagner Loduca Lima[1]

[1]Discipline of Ophthalmology, Centro Universitário FMABC - Santo André (SP), Brazil.
[2]Clinical Analysis Laboratory, Centro Universitário FMABC - Santo André (SP), Brazil.
[3]Department of Pharmaceutical Sciences, Universidade Federal de São Paulo (UNIFESP) – Diadema (SP), Brazil.

ABSTRACT

Diabetic Macular Edema is a major cause of visual impairment in economically active population, being responsible for a significant impact in quality of life in the affected population, as well as high costs to the health care system. Over decades, some studies have compared treatments using Laser, Anti-VEGF and intravitreous corticosteroids, establishing protocols to reach effectives therapies. Thus, it is essential an entire understanding of available therapies to reach the goal of disease control, in an individual basis and in a collective health care system, as efficient as possible.

Keywords: macular edema; diabetes mellitus complications; intravitreal anti-vegf injections; literature review.

INTRODUCTION

Diabetes mellitus (DM) is a pandemic with significant morbidity. One of its systemic complications is Diabetic Retinopathy (DR), which affects one in three people living with DM. In 2010, more than 92 million people had any form of DR, and 20 million had Diabetic Macular Edema (DME)[1].

DME is the leading cause of vision loss in the diabetic population[2]. The pathophysiology of DME is multifactorial and highly complex, including angiogenic and inflammatory factors, such as cytokines and vascular endothelial growth factor (VEGF), not being fully understood yet[3].

Since DME is highly prevalent and can be responsible for a heavy disease burden, affecting patients quality of life, many therapeutics approaches to disease control have been studied and proposed. Therapy options include intravitreal anti-VEGF injections, intravitreal corticosteroids injections, subthreshold micropulse laser (SML), and macular grid or focal laser photocoagulation[4,5].

Intravitreal anti-VEGF injections have been noticed to be more effective than laser therapies, being the major therapeutic approach since the 80s. Nowadays, the anti-VEGF drugs clinically available to treat DME are Ranibizumab, Aflibercept and Bevacizumab. The last has an off-label use. All three have been proven to be effective in the treatment of DME and in visual recovery, with no significant effectiveness difference between the three drugs[6,7].

The SML, however less effective, can be an alternative or adjuvant therapy option to anti-VEGFs. It has a proven effect in maintaining visual acuity and improving macular fluid[8,9]. SML delivers energy in short pulses, and rather than the destruction of photoreceptors, it causes retina pigment epithelium stimulation with no burning or scaring of retina[5].

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Corresponding Author: Vagner Loduca Lima - Discipline of Ophthalmology, Centro Universitário FMABC – Avenida Lauro Gomes, 2000 – Sacadura Cabral – CEP: 09060-650 - Santo André (SP), Brazil - E-mail: vagner@loduca.com.br

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Given the different approaches described to treat DME, the objective of this study was to review literature about and compare treatment options, guiding ophthalmologists clinical's decision when facing diabetic patients with DME.

METHODS

A PubMed search for studies describing DME pathophysiology, DR, anti-VEGF drugs, steroids for intravitreal injection, SML, and macular grid and focal laser photocoagulation were performed. Studies describing and comparing the diverse therapeutic approaches were selected and results summarized and reported.

RESULTS

40 manuscripts were reviewed and 30 selected to be reported. Epidemiologic and physiopathology studies about DME were selected to contextualize the topic. Comparative studies of different therapeutic approaches were then reported in chronological order to help understand the historic evolution of DME treatment. From the ETDRS, the first study to define clinically significant DME and introduce laser therapy, to up-to-date DRCR.net protocols of intravitreal anti-VEGF injections and the MEAD study about the use of the recent approved use of intravitreal corticosteroids are reported in this literature review.

DISCUSSION

The World Health Organization (WHO) estimates that, by 2025, the number of people living with DM, which today is 150 million people, will duplicate. DM is a pandemic and leads to significant morbidity, including impairment. One of its systemic complications is DR, which affects 33% of people living with DM. In 2010, more than 92 million people had any form of DR, and 20 million had Diabetic Macular Edema (DME). DME has an increasing prevalence, being today a major cause of visual impairment in the economically active population[10].

DME is the leading cause of vision loss in the diabetic population. There is an estimate that 29% of people living with diabetes for more than 20 years will develop DME[11]. Given its high prevalence and its expensive treatment, DME is nowadays a major public health problem[5].

The main risk factors for developing DME are disease duration, being known that after 20 years of disease, 28 to 29% of the affected population will develop DME; the severity of DR, being more common in the proliferative form; and need for insulin therapy, giving a 3 to 4 times higher risk[11].

Pathophysiology of DME is multifactorial and highly complex. The diabetic hyperglycemia leads to cell sorbitol accumulation, which, in turn, leads to osmotic damage to the cell. This osmotic damage affects cells' antioxidant defense, leading to free radicals' accumulation, and therefore secretion of VEGF as a cell response. The VEGF and others inflammatory factors release leads to vascular permeability increase and cellular oxidative stress, breaking the inner blood-retina barrier, and therefore leading to macular edema[12].

DR can also damage the outer blood-retina barrier, formed at the retinal pigment epithelial (RPE) cell layer, leading to lipid accumulation in the sub-retinal space, which also contributes to thickening of macular area[13].

Diabetic hyperglycemia also leads to thickening of retinal capillary basement membrane (BM). This BM thickening damages capillary pericytes, which are cells responsible for the development and architecture of blood vessels, leading to microaneurysms formation, and therefore plasma leakage to the intercellular media. In addition to increased vascular permeability VEGF mediated, diabetic vasculopathy leads to capillary dilation and hydrostatic pressure increase, contributing both to vascular homeostasis breakout, and therefore fluid leakage to retina. Given the pathophysiology, DME can therefore be found in areas of decreased vascular perfusion, in areas surrounding leaking microaneurysms, and ischemic areas[14,15].

A landmark study about DME was the Early Treatment Diabetic Retinopathy Study (ETDRS), which introduced the concept of clinically significant DME: retinal thickening at or within 500 microns or 1/3-disc diameter of center of macula, or hard exudates at or within 500 microns of the center of the macula with adjacent retinal thickening, or retinal thickening greater than 1 disc diameter in size which is within 1 disc diameter from the center of the macula[16].

A DME staging system was also proposed. Wilkinson *et al.* classified DME as mild: retinal thickening or hard exudates in posterior pole but distant from the center of the macula; as moderate: retinal thickening or hard exudates approaching the center of the macula but not involving the center; or as severe: retinal thickening or hard exudates involving the center of the macula[17].

Nowadays, imaging techniques are available to evaluate DME. Fluorescein Angiography (FA) and the Optic Coherence Tomography (OCT) are the most often used. On FA, DME is observed as a contrast leakage in the macular area due to exudation from the capillary network or from microaneurysms. When fluid accumulates in the Henle's fiber layer, there is formation of cystic spaces, which produces a petaloid aspect of hyper fluorescence named cystoid macular edema. Based on FA, DME can be diffuse, when there is increased vascular permeability, which is seen as a diffuse late macular hyper fluorescence, or can be focal, when leakage is from a microaneurysm, which is seen as a punctate hyper fluorescence[18].

The OCT allowed a more detailed classification of DME based on macular topography and retinal morphology. Based on OCT,

it is possible to observe diffuse retinal thickening, cystoid macular edema, subretinal fluid and vitreoretinal interface abnormalities. The OCT also allows making measurements of retinal thickness and analyzing retina's microstructure with great precision and reproducibility[19,20].

OCT has also been proven to be more sensible in detecting DME. Studies have shown that about 40% of DME detected by OCT is not identified in slit lamp fundus examination and up to 63% was not detected by FA[21].

Furthermore, OCT allows a better follow up of patients treating DME. According to the DRCR.net study, a central retinal thickness of one millimeter, which is only measured witch OCT, is considered the target when treating DME, being the most related parameter to visual acuity improvement. The OCT technology has been evolving, and nowadays an OCT Angiography (OCT-A) is commercially available. The OCT-A is able to measure retina's blood flow generating detailed angiographic images in a matter of seconds. This new imaging technology has added information to DR and DME pathophysiology, evidencing that vascular changes starts on retina's deep capillary plexus with microaneurysms formation. Besides, OCT-A is able to detect early sings of DME, such as the break of capillary plexuses integrity, allowing prompt treatment[22,23].

A clinical workup in the evaluation of diabetic patients is also important to determine his or her likelihood to develop DME, the visual prognosis and to choose the best available therapeutic approach. The treatment of DME is not limited to the eye, it will always include systemic disease control to achieve a better result. Strict glycemic control, avoiding hypoglycemia and hyperglycemia, blood pressure control, adequate lipid profile and normal renal function are the most important.

The treatment options for DME have evolved and widened through the years. From the first to the last, macular grid or focal laser photocoagulation, triamcinolone acetonide intravitreal injection, anti-VEGF intravitreal injection (Bevacizumab, Ranibizumab, and Aflibercept), dexamethasone intravitreal implant, subthreshold micropulse laser and posterior vitrectomy are nowadays available.

Macular grid or focal laser photocoagulation were the first-choice treatments for DME, improving visual acuity and macular anatomy. The macular grid is the choice for diffuse edema, being delivered throughout the macula with a lower energy than conventional laser photocoagulation. On the other hand, the focal laser photocoagulation is the choice for focal edema, being delivered to the leaking microaneurysm[16].

The ETDRS study concluded that macular laser treatment reduced the risk of moderate visual loss in more than 50% of patients with DME, mainly in those who had a central foveal thickening. Visual improvement was also observed, however the main benefit was to avoid vision loss. Eyes with severe vision loss had limited benefit in terms of visual acuity recovery[16].

The main side effect with macular grid or focal laser photocoagulation is scotoma formation, secondary to retinal scaring due to laser photocoagulation, which can have an enlarging tendency though years.

Nowadays, first choice treatment for DME is intravitreal anti-VEGF injection, which acts inhibiting VEGF isoforms. There are three commercially available anti-VEGF drugs used in ophthalmology: Bevacizumab (Avastin®), a monoclonal antibody against VEGF-A, Ranibizumab (Lucentis®), a monoclonal antibody fragment against VEGF-A, and Aflibercept (Eyelia®), a soluble decoy receptor that binds VEGF-A, VEGF-B and placental growth factor. It is important to note that the Bevacizumab is not approved by the Food and Drug Association (FDA) for intraocular use, being used off-label in the treatment of DME.

Studies have been conducted to evaluate anti-VEGF efficacy and compare them to each other and to others available therapies. Bevacizumab has been studied by the Protocol H, which compared efficacy of Bevacizumab intravitreal injection to laser treatment and to combined therapy of laser plus Bevacizumab. Protocol H concluded that intravitreal Bevacizumab injection reduced macular thickness more than laser treatment, however its effects on visual acuity were not compared[24].

Ranibizumab was studied on Protocol I, which compared efficacy of intravitreal Ranibizumab injection combined with macular grid or focal laser photocoagulation to laser alone and to laser plus intravitreal Triamcinolone Acetonide injection for treatment of DME. Protocol I concluded that in the first two years Ranibizumab plus laser was the most effective treatment in reducing macular edema, and that Triamcinolone Acetonide plus laser was more effective than laser alone, when considering pseudophakic eyes[25].

The RESTORE study compared the use of Ranibizumab alone to Ranibizumab plus macular laser and to macular laser alone in the treatment of DME. The study was followed up patients for 12 months and concluded that Ranibizumab alone was the most effective treatment when considering both anatomical criteria (reduction in macular thickness) and functional criteria (increase in visual acuity)[26].

Ranibizumab has also been studied by the RISE AND RIDE study. This multicentric, placebo controlled, two-year follow-up study compared intravitreal Ranibizumab injection of 0,3 mg to 0,5 mg for the treatment of DME. RISE AND RIDE study concluded that Ranibizumab treated patients had a better anatomic response and gained more letters compared to sham treated group. This better response was maintained if treatment continued and there was a lower risk of visual loss in these patients[27].

The BOLT study compared ETDRS laser protocols to intravitreal Bevacizumab injection in the treatment of DME. BOLT study found that Bevacizumab treated group gained in average eight letters on ETDRS chart compared to a loss of 0.5 letter in the laser

treated group. In the 12-month follow-up period, the decrease in the macular thickness was higher in the Bevacizumab treated group. In the 24-month follow-up period, Bevacizumab treated group gained in average nine letters on ETDRS chart compared to a gain of 2.5 letters in the laser treated group, proving the superiority of Bevacizumab in the treatment of DME, both anatomically and functionally[28].

The Protocol T, a DRCR.net study, included patients with OCT proven DME and visual acuity between 20/32 and 20/320. The study compared the intravitreal injection of Bevacizumab to Ranibizumab and to Aflibercept. Protocol T proved that all three anti-VEGF were effectives in the treatment of DME, being able to improve visual acuity and to reduce macular thickness, with a reducing need for injections in the second year of treatment. In eyes with visual acuity between 20/32 and 20/40, there was a gain of eight letters on ETDRS charts in all three groups, and the gain was maintained for two years. In eyes with visual acuity of 20/50 or lower, Aflibercept was superior to the others anti-VEGFs in promoting gain of letters in the first year of treatment. However, in the second year, Aflibercept and Ranibizumab had equivalent results, and both superior to Bevacizumab[7].

Protocol W is currently being conducted with a planned deadline for 2022. Protocol W is evaluating anti-VEGF use in visual loss prevention in patients with non-proliferative DR and DME.

Intravitreal corticosteroid injection is also an option in the treatment of DME, mainly in anti-VEGF non-responsive cases. Nowadays, the clinically available corticosteroids for intravitreal use are the Triamcinolone Acetonide and the 0,7 mg Dexamethasone Intravitreal Implant (Ozurdex®). The most common indication is persistent and anti-VEGF non-responding DME, and the main side effects are cataract formation and intraocular pressure rise.

The DRCR.net study also compared intravitreal Triamcinolone Acetonide in a 1 mg dose and 4 mg dose to a control group. Treated group had an improvement on macular thickness, and cataract formation and intraocular pressure rise were also observed[24].

The Dexamethasone Intravitreal Implant was investigated by the MEAD study. Patients with DME were randomly assigned to 0,35 mg intravitreal dexamethasone implant, or 0,7 mg intravitreal dexamethasone implant, or sham group. At the end of two years, 18,4%, 22,2% and 12% of patients had gained at least 15 ETDRS letters of visual acuity at the three groups, respectively. Besides that, the time of visual improvement was significantly faster in the dexamethasone treated groups compared to sham group[28].

The subthreshold micropulse laser is an option to the conventional photocoagulation laser, because unlike the last, the SML does not leads to retinal burning or scaring. The SML leads to retina pigment epithelium stimulation, and therefore absorption of macular fluid, being used as an adjuvant to anti-VEGF or as an alternative to non-responsive cases. Studies comparing SML to conventional laser concluded that both had a similar effect on reducing macular thickness, with SML leading to lower retinal damage[29-31].

There is still the possibility of posterior vitrectomy for chronic and refractory cases of DME, mainly when there is a tractional component on macular edema, like on epiretinal membrane[32].

Conclusion

DME is the leading cause of visual loss in people living with diabetes. Early ophthalmologic specialized assistance associated to clinical control of DM are the most important factors to patient recovery. Given the wide range of treatment options to DME, updated and comprehensive knowledge about this topic is essential to the retina specialist to deliver an individualized and efficient treatment for patients.

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