

Overview of Therapies for Diabetic Macular Edema

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ISSN: 2578-0263



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Submission:  June 04, 2019

Published:  June 14, 2019

Volume 3 - Issue 1

How to cite this article: Gabriela Y, Italia A R, Gustavo A, Adrian H, Tania V. Overview of Therapies for Diabetic Macular Edema. *Interventions Obes Diabetes*. 3(1). IOD.000552.2019.
DOI: [10.31031/IOD.2019.03.000552](https://doi.org/10.31031/IOD.2019.03.000552)

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Abstract

Diabetic retinopathy is the most common microvascular complication of diabetes mellitus. The direct cause of this irreversible loss of sight is diabetic macular edema, which affects more than 126 million people worldwide. In order to confirm the diagnosis, specific studies, such as fluorescein angiography and optical coherence tomography (OCT), should be carried out to determine the degree and type of edema. We review recent efficacy and safety data for the therapies currently existing to reduce progression and recover vision in Diabetic Macular Edema. In addition, there is the high cost of treatment of macular edema, as well as the risks involved in the application of drugs used for this disease. We therefore decided to carry out this review in order to evaluate the effectiveness of different therapies for the management of diabetic macular edema. The growing controversy over treatment for this complication has led to a constant conflict over what the best therapeutic option for the affected individuals is. Alternatives for supplementation have also been sought out with studies that support the efficacy of their use in treating this disease.

Keywords: Anti-VEGF; Diabetic Retinopathy; Lutein; Macular Edema; Oxidative-Stress; Therapies

Keywords: OCT: Optical Coherence Tomography; DR: Diabetic Retinopathy; DME: Diabetic Macular Edema; VEGF: Vascular Endothelial Growth Factor; DRCR: Diabetic Retinopathy Clinical Research; ILM: Internal Limiting Membrane

Introduction

In 2017, the number of diabetics in the world was more than 451 million [1]. In Mexico, there are more than 12 million people diagnosed with Type 1 or 2 Diabetes [2]. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes [3] and occurs in 47.26% of the population with type 1 diabetes mellitus, and in 26.49% of type 2 diabetics [4]. Diabetic macular edema (DME) is the leading worldwide cause of acquired loss of vision in middle aged, and therefore economically active, people [5]. It affects one in 15 people with diabetes, resulting in more than 20 million cases worldwide [6]. Studies conducted on the population of Mexico City reported that the proportion of diabetics with DME who have visual impairment at the time of diagnosis is 69.4% [7]. Certain studies in America report a prevalence of Diabetic Retinopathy in 33.3% of patients (29.9% with Non-Sight Threatening Retinopathy and 3.4% with Sight Threatening Retinopathy, more than half of which suffer from macular edema) [8,9], (Figure 1).

The presence of retinal edema is defined as an increase in interstitial fluid at tissue level, which causes a thickening of the central retina (macula). This fluid increase can be intracellular or extracellular, which induces an alteration of the external blood-retinal barrier [10]. Among the factors that predispose people with diabetes to visual damage are hyperglycemia and retinal ischemia. Through a series of pathophysiological processes, there is stimulation of the synthesis and secretion of vascular endothelial growth factor (VEGF) and interleukin 6 (IL-6) [11]. These factors act directly on the tight junctions of endothelial cells, decreasing protein content or increasing phosphorylation; altering the paracellular permeability [12].

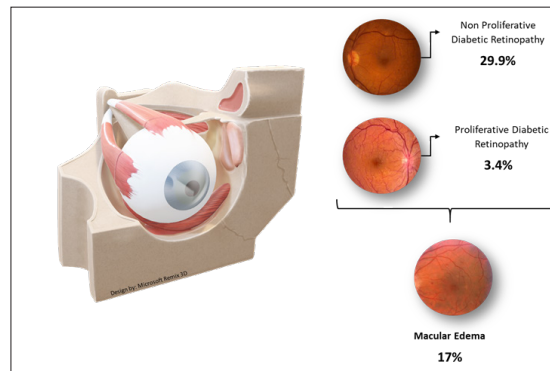


Figure 1: Prevalence of diabetic retinopathy (non-proliferative/ proliferative retinopathy).

Treatment

Existing therapies can be divided into 3 types: Pharmacological, by administering anti-VEGF drugs (Ranibizumab 0.3 or 0.5mg, Bevacizumab 1.25mg, or Aflibercept, 2mg) or corticosteroids (Dexamethasone Implant, Fluocinolone Acetonide and Triamcinolone Acetonide); Interventions, such as vitrectomy and

the application of conventional or pulsed lasers; Emerging therapies of natural origin, such as lutein in capsules or pycnogenol (French pine extract) [13], (Figure 2). According to the International Council of Ophthalmology’s Clinical Guidelines for the management of ocular pathology of the diabetic: The treatment of macular edema in high-resource countries, according to the severity of the retinal manifestations and the clinical picture, is as follows:

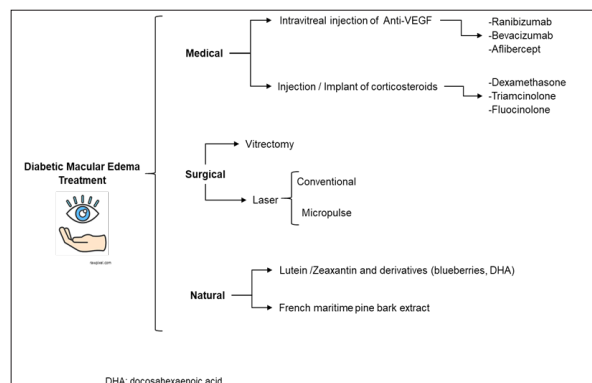


Figure 2: Flow chart of the main treatments for diabetic macular edema.

a. DME with central damage and good visual acuity (better than 20/30): Careful follow-up with anti-VEGF treatment or laser photocoagulation with anti-VEGF, if necessary.

b. DME with central commitment and associated vision loss (20/30 or worse): Intravitreal anti-VEGF treatment. For persistent thickening of the retina, consider laser treatment after 24 weeks. Treatment with intravitreal triamcinolone may also be considered, especially in pseudophakic eyes. For low/medium resource countries, focal laser is preferred if intravitreal injection of anti-VEGF drugs is not available or if a monthly follow-up is not possible [14].

Focal macular laser

For many years the main treatment for DME was focal laser, sometimes supplemented with corticosteroid injections. Laser treatment reduced the risk of moderate visual loss in approximately 50% of the patients, but only 3% of the eyes displayed improved vision (<3 lines of visual acuity) and a substantial proportion of

people had no response to treatment [15]. In the study conducted by Mitchell et al. [16], in which 345 patients with DME participated, a reduction of micrometers (µm,) of the edema measured by optical coherence tomography (OCT) was observed. In the laser monotherapy there was a decrease of -61.3 µm (p ≤ 0.001). However, in the same study, an anti-VEGF drug was also administered to another group and a further group underwent a combination of both therapies. It was shown that the combination of laser therapy with anti-VEGF was more effective than laser monotherapy on its own, showing a decrease of -128.3 µm (p ≤ 0.001). A significantly higher proportion of patients had an initial BCVA (Visual Corrected Acuity) score of ≥15 (Snellen equivalent 20/500) and a subsequent score of > 73 (Snellen equivalent of 20/40) with single laser (8.2% and 23.6%); Ranibizumab (22.6% and 53%, respectively) and Ranibizumab+laser (22.9% and 44.9%) [16]. It was concluded that laser treatment combined with an anti-VEGF drug is more effective than laser therapy on its own in rapidly improving and maintaining Visual Acuity in patients with visual impairment due to Diabetic Macular Edema [17], (Table 1).

Table 1: Timeline of the main clinical trials comparing the level of efficacy in the improvement of visual acuity and macular thickness reduction of the different current therapies: Anti-VEGF [40, 42, 43, 16, 23, 19, 44], Corticosteroids [28,23], Supplements [40, 41, 34] and therapies combined with laser [42, 16].

Author	Year	Country	n	Period	Treatment										Results				
					Laser	Ranibizumab	Bevacizumab	Aflibercept	DEX Implant	Triamcinolone	DHA	Lutein	Zeaxanthin	Me-sozeaxanthin	Vi-ta-mins	BCVA	Macular Thickness (µm)	Plasma concentrations (µg/mL)	
María La-Fuente et al [40]	2017	Spain	62	2 years	●	● 0.5 mg					● 350 mg	● 3 mg	● 0.3 mg			DHA Group: ↓169 ± 122 (p<0.001). ETDRS letters= ↑12.0 ± 5.9 Ranibizumab Group: ↓140 ± 124 (p<0.066)			
M. Moschos et al [41]	2017	Greece	60	2 years								● 10 mg	● 2 mg	● 10 mg		Without changes (≥ 9/10 letters)	Right eye: ↑5.4 ± 0.6 (p<0.001) Left eye: ↑6.3 ± 0.8 (p<0.001)		
Hu BJ et al [34]	2011	China	90	3 months								● 6 mg	● 0.5 mg		cpd= ↑0.45 ± 0.334 (p<0.001)			DR Group: ↑ L/Z (0.5409/0.2816). Control Group: L/Z= 0.0701 / 0.0224 (p=0.0001)	
J. Elman et al [42]	2012	U.S.A	291	3 years	●	● 0.5 mg									≥10 letter gain: Ranibizumab + Laser: 42%; Ranibizumab: 56% (p= 0.02)	Ranibizumab + Laser: ↓152 ± 165; Ranibizumab: ↓174 ± 139 (p= 0.56)			

Cam- pos Polo etal [43]	2018	Spain	15	1 year														ETDRS letters= ↑14.9 ± 6.5 (p< 0.001).	↓231.5 ± 32 (p< 0.001).
Paul Mitch- ell etal [16]	2011	U.S.A	345	1 year			● 0.5 mg											Ranibi- zumab + Laser: ↓152 ± 165; Ranibi- zumab: ↓174 ± 139 (p= 0.56)	Ranibi- zumab + Laser: ↓152 ± 165; Ranibi- zumab: ↓174 ± 139 (p= 0.56)
S. Boyer etal [28]	2014	U.S.A.	1048	3 years					● 0.7 mg/ 0.35 mg									↑ ≥ 15 letters DEX implant 0.7 mg (p< 0.001); DEX Implant 0.35 mg (p= 0.005)	DEX implant 0.7 mg; ↓111.6; DEX implant 0.35 mg; ↓107.9 (p< 0.001)
Ja- cinto Jorge etal [23]	2017	Mexico	17	24 weeks			● 0.3 mg			● 0.7 mg	● 1 mg							Ranibi- zumab + DEX Implant: ↓140 (p< 0.05) Ranibi- zumab + Triam- cinolone: ↑ 23 letters (p< 0.05)	Ranibi- zumab + DEX Implant: ↓140 (p< 0.05) Ranibi- zumab + Triam- cinolone: ↑23 letters (p< 0.05)
J. Blind- er etal [19]	2017	U.S.A.	156	6 months			● 0.5 mg			● 1.25 mg	● 1 mg							ETDRS let- ters= ↑1.0 to 1.3 lines (p< 0.001)	after of the first 10 in- jections: ↓45 to 83 (p≤ 0.015)
Shi- mizu etal [44]	2017	Japan	76	6 months			● 0.5 mg				● 1 mg							Ranibi- zumab Group: ↓70 (p= 0.0053); Afliber- cept Group: ↓ 82 (p< 0.0001)	Ranibi- zumab Group: ↓70 (p= 0.0053); Afliber- cept Group: ↓ 82 (p< 0.0001)

Anti-VEGF injections

Anti-VEGF treatments achieved great popularity because they act by reducing angiogenesis and vascular permeability, processes that cause the regression of diabetic neovascularization [18]. Blinder et al. [19], in a retrospective study with 156 patients who received more than 3 injections of anti-VEGF (627 injections of Bevacizumab, 594 of Ranibizumab and 1 of Aflibercept), found that the percentage of patients with BCVA of 20/40 or better and macular thickness <250 μm increased from 16.4% to 38.9% after the first 10 injections. In addition, more than 15% of people had achieved BCVA 20/40 and 22% decreased their macular thickness. However, the results of this study conclude that a significant percentage of patients treated with intravitreal anti-VEGF did not achieve 20/40 or more visual acuity after anti-VEGF injection, possibly because this medication does not inhibit all inflammatory cytokines of the EMD [19] (Table 1). In the VISTA and VIVID studies, a significant improvement in visual acuity was reported ($p \leq 0.001$) compared to the laser. The proportion of eyes that gained ≥ 15 letters from the beginning in week 148 was 42.9% with 2 mg of aflibercept every 4 weeks, 35.8% with a dose of 2mg every 8 weeks of Aflibercept and 13.6% with laser alone ($p \leq 0.001$). [20].

The Diabetic Retinopathy Clinical Research Network (DRCR Protocol) compares the effects of the three antiangiogenic agents and reports that there are no significant differences between them; concluding that all three intravitreal anti-VEGF agents have acceptable ocular and systemic safety profiles to support their use as first-line treatment for DME, when accessible, over observation, focal/grid laser or corticosteroids with or without concomitant laser treatment [21]. Patients who respond suboptimally to treatment with anti-VEGF may need additional therapy with corticosteroids [22]. Jacinto et al. [23]; affirms that this combination improved visual acuity, significantly reduced central macular thickness and did not significantly increase intraocular pressure in patients with diabetic macular edema. In their clinical trial, 17 patients received Anti VEGF injections and corticosteroid implants for 24 weeks. An improvement in 28-letter ($p \leq 0.05$) visual acuity was observed on average, accompanied by a reduction of 158 μm ($p \leq 0.05$) in central macular thickness and an increase in intraocular pressure of 1mmHg. One of the patients underwent cataract surgery and one participant had increased intraocular pressure of more than 10 mmHg, which was controlled with the addition of an ocular hypotensive [23].

Corticosteroids

Corticosteroids are drugs that inhibit macrophages that release angiogenic growth factors, in addition to diminishing the expression of the major histocompatibility complex (MHC-II) in the superficial layers of the retina [24,25]. However, their use has been decreasing due to concerns about cataract formation and increased intraocular pressure [26]. Studies report that up to a third of patients treated with intravitreal implants of Dexamethasone (DEX) achieve a vision of 20/40 after their first implant, and the benefit of the treatment is maintained in the long term [27]. This implant has shown efficacy and has had an acceptable safety profile as reported by Boyer et al. [28]. In this study, 1048 patients received a Dexamethasone

implant of 0.7 mg, 0.35 mg and a placebo group for 3 years. The percentage of patients with ≥ 15 -letter improvement in BCVA from baseline at study was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than the sham implant (12.0%; $p \leq 0.018$). Mean average reduction in macular thickness from baseline was greater with the DEX implant 0.7 mg (-111.6 μm) and DEX implant 0.35 mg (-107.9 μm) than sham (-41.9 μm , $p \leq 0.001$). Rates of cataract-related adverse effects in phakic eyes were 67.9% (DEX implant 0.7 mg), 64.1% (DEX implant 0.35 mg), and 20.4% in the sham group. Increases in intraocular pressure were usually controlled with medication or without therapy; only 2 patients (0.6%) in the DEX implant 0.7 mg group and 1 (0.3%) in the DEX implant 0.35 mg group required trabeculectomy [28].

There is scientific evidence that corticosteroids are a good option for persistent macular edema, as in the study by McCluskey et al. [29] injections of 0.2 $\mu\text{g/day}$ fluocinolone acetonide [FAC] were performed intravitreal implant in patients with persistent or recurrent DME and a reduction of the macular volume was observed in 89% of the eyes, with a statistically significant ($p \leq 0.001$). The average central retinal thickness reduction for all 18 eyes was statistically significant, decreasing from 444 μm at baseline to 359 μm after the FAC implant ($p \leq 0.001$). In 90% of eyes, visual acuity was stable throughout the follow-up period. Despite being a safe therapy, it is necessary to take into account side effects of intravitreal steroids, such as increased intraocular pressure and cataracts. Therefore, it is necessary to administer them with caution and make periodic revisions to avoid their occurrence (Table 1).

Vitrectomy

People with diabetes very frequently have vitreomacular traction (TVM) or epiretinal membranes (ERM) on the macula. The pull-on retinal vessels increase their permeability and produces tractional diabetic macular edema (EMDT). Surgery is reserved for cases in which there is vitreomacular traction, because it is in these cases where vitrectomy is effective [30]. The vitrectomy with internal limiting membrane (ILM) peeling has efficacy for laser-insensitive patients or patients did not respond to anti-VEGF or steroids substances and is the last method for the therapy of refractory DME [31]. Gandorfer et al. [32] suggested that ILM peeling led to an earlier and greater decrease of retinal thickness or to an earlier and better VA and can decrease the risk of subsequent ERM formation by eliminating a scaffold for proliferating cells [32].

Lutein supplements

Emerging therapies of natural origin, due to their antioxidant effect, have been shown to be more effective if they are administered as adjuvant treatment and prophylactically [33]. However, they maintain an efficacy similar to or even greater than that of conventional lasers. Studies have been conducted with Lutein oral supplementation, as reported by Hu et al. [34], in which 30 individuals with Non-Proliferative diabetic retinopathy were treated with 6mg/d and zeaxanthin 0.5mg/day for three months. There was another group of 30 subjects without supplementation and a Control group. Visual acuity and foveal thickness were recorded at the beginning and 3 months after supplementation.

Significant improvement in visual acuity was observed after the medication, compared to the BCVA baseline ($F = 18,698, p \leq 0.001$). Furthermore, the foveal thickness after Lutein and Zeaxanthin supplementation was significantly decreased (mean $286.50 \pm 134.185, p \leq 0.05$) [34] (Table 1).

Systemic treatment

Systemic Agents to Treat DME: Hypoglycemic Agents (Insulin Therapy, Thiazolidinediones Biguanides) [35]; Hypolipidemic Agents (Fibrates, Statins) [36]; Antihypertensive Agents (Angiotensin-2 Converting Enzyme Inhibitors, Angiotensin-2 Receptor Blockers) [37]; Antiplatelet Agents [38]; Ruboxistaurin and Somatostatin Derivatives [39]. These types of drugs, used in chronic and autoimmune diseases, have been tested to slow the progression of diabetic retinopathy. However, they require more scientific sustenance to be considered effective options.

Conclusion

We continue to search for an effective monotherapy to treat central visual loss in those who are found to have Diabetic Retinopathy, complicated by DME. According to the options that exist today, it is concluded that all demonstrate a certain degree of effectiveness, because the mechanism of action is different in each one. However, the administration of combination therapy with anti-VEGF [40-44] and laser or with corticosteroids is recommended, as it results in greater improvement of visual acuity and decrease in macular thickness. General recommendations in general for the choice of therapy should be based on three fundamental aspects: the level of visual acuity, the degree of macular thickness and the area of visual commitment. The availability of each drug sometimes results in the choice being what is available to the patient, rather than what is most appropriate. The high costs, application technique and myths around each therapy are some of the limitations that impede their prescription.

Limitation

More studies are required in which a comparison is made between emerging therapies, such as micropulsed laser vs early administration of Lutein. Finally, emerging therapies, such as the oral administration of supplements that decrease macular degeneration associated with age, plant derivatives and other components, provide a prophylactic and preventive option of great help that should be implemented in a timely manner in all people suffering from diabetic retinopathy, given that prevention of DME must always be the first priority.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgment

We thank optometrist Edgar Lara Cibrian for contributing for their knowledge in the subject.

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