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Research Article

OVERVIEW OF CURRENT TREATMENT IN DIABETIC MACULAR EDEMA

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A R T I C L E I N F O

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A B S T R A C T

Diabetic macular edema is a leading cause of vision impairment among people within the working- age population. This review discusses the pathogenesis of diabetic macular edema and the treatment options currently available for the treatment of diabetic macular edema, including for focal/grid photocoagulation, intravitreal corticosteroids and intravitreal anti-vascular endothelial growth factor agents.

INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of vision loss of working-age adults, and diabetic macular edema (DME) is the most frequent cause of vision loss related to diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy[1] found the 14-year incidence of DME in type I diabetics to be 26%. Similarly the Diabetes Control and Complications Trial (DCCT)[2] reported that 27% of type I diabetic patients develop DME within 9 years of onset.

Diabetic macular edema is diagnosed clinically by stereoscopic slit lamp biomicroscopy using preferably a contact lens for fundus evaluation.

Flourescein angiography is useful for evaluating the severity of the dysfunction in the blood- retinal barrier, however, it does not reliably quantify the degree of fluid accumulation in the retina.

The optical coherence tomography (OCT) is a modality that helps in the objective assessment of diabetic macular edema. Moreover, OCT is found to be useful in the morphological description of diabetic macular edema.

Pathogenesis of Diabetic Macular Edema

The pathogenesis of diabetic macular edema involves the breakdown of the blood-retinal barrier (BRB), which is composed of an inner BRB and an outer BRB. Diabetic macular edema is thought to be caused primarily by the breakdown of the inner BRB, though evidence does exist that outer BRB dysfunction may play a role in DME (reviewed in). Breakdown of the BRB allows for extravasation of proteins and other solutes from capillaries into the extracellular space. This causes a shift in the balance of hydrostatic and oncotic pressure, favoring the accumulation of fluid within the extracellular space and the development of macular edema.

Some of the earliest changes seen histologically in the diabetic retina are leukocyte adhesion to capillaries as well as accumulation of advanced glycation end products (AGEs). These changes contribute to activation of inflammatory mediators and endothelial cell death. Endothelial cell death contributes to the breakdown of the BRB and can lead to increasing ischemia. In addition to cell loss, breakdown of endothelial cell tight junctions also occurs (reviewed in). Another histologic change associated with the development of diabetic retinopathy is loss of pericytes, which are cells that are associated with capillaries and are located outside of the blood-retinal barrier. Amongst their functions are the stabilization blood vessels. Loss of pericytes may be related to accumulation of AGEs and to the presence of inflammatory mediators and is associated with the formation of microaneurysms and the breakdown of the BRB. The various treatment modalities for diabetic macular edema are described below.

Laser Treatment for Csme

The ETDRS study demonstrated that laser treatment reduced the risk of moderate visual loss (loss of 3 or more lines in snellens equivalent / 15 or more letters on ETDRS chart) and improved the chances of visual improvement in patients with CSME.

As noted above, laser photocoagulation[3] had been the mainstay of treatment for DME for almost for the past 25 years, since

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the publication of photocoagulation results from the ETDRS. The mechanisms of action of focal/grid laser are not well understood and are not discussed in this review. However, the technique involves placement of light, small (around 50 micron) laser burns only within thickened areas of the macula, including direct (focal) treatment of microaneurysms as well as spots scattered approximately two to three burn widths apart (grid) within other areas of edema not accounted for by microaneurysms. While it previously was used as a monotherapy, focal/grid laser is used in conjunction with anti-VEGF therapy, typically when DME persists and is not continuing to improve after at least 6 months of monthly injections of anti-VEGF therapy. It is added to anti-VEGF therapy if the eye has not had complete laser (focal/grid) treatment to all areas of microaneurysms within areas of edema and grid treatment to all other areas of edema, provided it has been at least 3 to 4 months since any prior focal/grid laser. Macular laser for DME likely will continue to be part of the management of DME in selected patients, especially in the developing world, as its lower cost and less intensive management requirements compared to newer treatment modalities still make laser photocoagulation a preferred therapy in some clinical settings.

Treatable Lesions

1. Focal leaks situated more than 500 microns away from the centre of macula causing hard exudates or retinal thickening.
2. Focal leaks situated within 300- 500 microns from centre of macula causing hard exudates or retinal thickening.
3. Areas having diffuse leakage from capillaries and microanuerysms.
4. Capillary avascular areas other than foveal avascular zone not treated previously.

Newer laser technologies include subthreshold diode-laser micropulse technology and selective retina therapy (SRT), which aims at minimizing retinal and RPE tissue damage.

Corticosteroids

Steroid agents are also increasingly being used for the treatment of DME. Triamcinolone, fluocinolone, and dexamethasone are some examples and can come in the form of intravitreal injections or implants.

Pharmacology

Corticosteroids have been shown to inhibit VEGF and other cytokines and growth factors, thereby regulating endothelial cell tight junctions. In addition, they inhibit prostaglandin and leukotriene synthesis, which results in a local reduction of inflammatory mediators. The resultant antiinflammatory effect contributes to the reduction of edema. Increased diffusion by modulation of calcium channels could also account for the efficacy of the corticosteroids in reducing macular edema.

Ivta In Diabetic Macular Edema

Intravitreal injection of corticosteroids (triamcinolone acetonide), constitutes a newer, less destructive treatment modality in the management of diabetic macular edema.

The rationale for the use of coticosteroids in the treatment of diabetic macular edema follows from the observation that the breakdown of the blood retinal barrier leads to the edema[4] and is in part mediated by Vascular endothelial growth factor (VEGF).

The efficacy of various methods of ocular corticosteroid injection has always been a matter of debate. Sub-Tenon's injections[5] when compared to intravitreal injections have the disadvantage of probably a decreased drug penetration through the sclera and choroid and a rapid removal of the drug by the choroidal circulation after penetration with the resultant short duration of action.

4 mg in 0.1 ml dose of triamcinolone is more popular basically, owing to convenience and the fact that a 0.1 ml volume of the drug in the vitreous cavity is well tolerated. There are no data that support this dosage over other alternative doses. The vehicle contains 6.9 mg sodium chloride for isotonicity, 15 mg benzyl alcohol as a preservative, 7.5 mg carmellose sodium and 0.4 mg polysorbate 80.

There are however certain serious complications that could occur due to the injection, such as glaucoma[6], cataract, endophthalmitis[7], and pseudoendophthalmitis. In order to avoid ocular toxicity, some centers inject only 1 mg of triamcinolone with 4 mg which is reserved for reinjections. All these complications are apart from the risks of retinal detachment and vitreous hemorrhage that are inherent to any intravitreal injection.

The landmark study by Martidis *et al*[8], was a prospective, noncomparative, interventional case series involving sixteen eyes with clinically significant macular edema (CSME) that failed to respond to at least two previous sessions of laser photocoagulation. At least 6 months after initial laser therapy, the response was measured by clinical examination and optical coherence tomography (OCT). Eyes with a residual central macular thickness of more than 300 microns (normal central macular thickness: 200 microns) and significant visual loss from the baseline were administered an intravitreal injection of 4 mg in 0.1 ml of triamcinolone acetonide. Mean improvement in visual acuity was 2.4, 2.4 and 1.3 Snellen lines at the 1, 3 and 6-months of follow-up respectively. The central macular thickness as measured by OCT decreased by 55%, 57.5% and 38%, respectively, over these same intervals from an initial pretreatment mean of 540.3 (± 96.3) microns. The researchers attributed more significant reduction in edema as compared to the improvement in visual acuity, which may be due to the injection being given after the chronic edema had already caused severe dysfunction. They hence suggested an early injection in severe cases.

Triamcinolone acetonide is increasingly being employed in pars plana vitrectomies, especially in complicated surgeries in diabetic eyes with recalcitrant macular edema.

Steroid Implants

Intravitreal steroids can also be administered in the form of implants, which have the advantage of sustained release of the drug. An intravitreal fluocinolone acetonide implant[9] has been shown to result in better outcomes as compared to MLP. At 2 years after implantation, a greater proportion of eyes had ≥15-letter increase in BCVA and significant resolution of macular thickening. However, at 3 years, the results were comparable to those with laser.

The bevacizumab versus intravitreal dexamethasone[10] for diabetic macular edema (OZURDEX) study compared the

efficacy of intravitreal bevacizumab with an intravitreal dexamethasone implant. At 12 months, the two treatments resulted in similar visual acuity outcomes while the key differences were that the intravitreal dexamethasone implant resulted in significantly greater reduction in CMT with the need for far fewer injections.

Another clinical trial comparing intravitreal dexamethasone implant in eyes with DME refractory to intravitreal bevacizumab resulted in a significant reduction in CMT and improvement in BCVA up to 3 months after implantation. However, the changes were no longer significant at 4 months.

Anti VEGF

Administration of VEGF inhibitors delays follicular development and suppresses luteal angiogenesis in primates. VEGF-164 blockade led to a significant inhibition of pathological Neovascularization with little or no suppression of revascularization and physiological Neovascularization[11].

Intravitreal Anti-VEGF

VEGF has inflammatory properties and is found to play a role in pathogenesis of DME by increasing capillary permeability. Anti VEGF agents help in restoring the normal permeability of blood retinal barrier.

Ranibizumab and bevacizumab are anti-VEGF agents that bind to all VEGF isoforms and fragments. Aflibercept, the latest newcomer to the market, is a recombinant protein that also binds all VEGF isoforms and fragments. Pegaptanib sodium (Macugen) is an RNA aptamer that selectively binds the VEGF-165 isoform, believed to be the main isomer responsible for DME.

Avastin (Bevacizumab)

Bevacizumab, recombinant, humanized, monoclonal antibody against VEGF has been used in diffuse type of macular edema where other treatment have failed. It was approved by the United States Food and Drug Administration on 26th February 2004 as a first line treatment of metastatic colorectal cancer.
AVASTIN (bevacizumab) is a clear to slightly opalescent, colourless to pale brown sterile solution for intravenous (IV) infusion. AVASTIN is available in 100 mg and 400 mg single dose vials containing 4 mL and 16 mL, respectively of bevacizumab (25 mg/mL).

AVASTIN is an antineoplastic agent containing the active ingredient, bevacizumab. Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps.

AVASTIN (bevacizumab) inhibits the binding of VEGF to its receptors, Flt-l and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth.
As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model[12]. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (VC), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

Avastin injection in diabetic macular edema

Haritoglou C and *et al.*[13], 2006 evaluated the efficacy of bevacizumab for the treatment of diabetic macular edema in 51 consecutive patients (26 females and 25 males; mean age, 64 years) with diffuse diabetic macular edema. Inclusion criteria were determined independently of the size of edema, retinal thickness, visual acuity, age, metabolic control, type of diabetes, or previous treatments beyond a 6-month period.

All patients completed 6 weeks of follow-up; 23 (45%) completed 12 weeks of follow-up. Sixteen patients (70%) had received at least two intravitreal injections. All patients had undergone previous treatments, such as focal laser therapy (35%), full-scatter panretinal laser therapy (37%), vitrectomy (12%), and intravitreal injection of triamcinolone (33%). The mean diameter of the foveal avascular zone was 503 micro m, with 49% with values of >500 micro m. At baseline, mean visual acuity +/- SD was 25.88 +/- 14.43 ETDRS letters (0.86 +/- 0.38 logMAR of Snellen letters). Mean central retinal thickness by optical coherence tomography +/- SD was 501 +/- 163 micro m (range, 252-1,031 micro m). Mean visual acuity +/- SD increased to 0.75 +/- 0.37 logMAR of Snellen letters at 6 weeks after injection (P = 0.001), with some regression to 0.84 +/- 0.41 logMAR of Snellen letters after 12 weeks. Changes in ETDRS letters were not significant throughout follow-up. Mean retinal thickness +/- SD decreased to 425 +/- 180 micro m at 2 weeks (P = 0.002), 416 +/- 180 micro m at 6 weeks (P = 0.001), and 377 +/- 117 micro m at 12 weeks (P = 0.001). Changes of retinal thickness and visual acuity correlated weakly (r = -0.480 and P = 0.03 at 6 weeks; r = -0.462 and P = 0.07 at 12 weeks).

The ranibizumab[14] for edema of the macula in diabetes randomized, controlled trial (RCT) compared ranibizumab alone, laser alone, and combination therapy for DME and at 6 months after treatment, ranibizumab resulted in a significant improvement in BCVA. Between 2 and 3 years after treatment, there were still significant improvements in mean BCVA. The effectiveness of ranibizumab might be explained by its ability to strongly suppress aqueous VEGF levels, which has been shown to last for an average of 33.7 days, and even up to 16 months. Furthermore, the extent of suppression does not appear to be affected by baseline VEGF levels.

However, anti-VEGFs may have their disadvantages, especially in terms of anatomical outcomes. Macular swelling is likely to recur after intravitreal anti-VEGF, requiring repeat retreatments. This is more likely with bevacizumab, given its relatively short intravitreal half-life. A possible alternative could be the use of laser to target leaking microaneurysms after the administration of bevacizumab, which has been shown to result in greater improvements in BCVA and CRT, as well as reduce the number of injections needed.

CONCLUSION

Macular laser photocoagulation has been the standard treatment for DME during the past 2 decades. Although it can reduce the risk of moderate visual loss in CSME, only a few

patients can experience visual improvement after treatment. The anti-VEGF antibody, ranibizumab, has shown a greater potential than laser treatment in improving visual outcomes of patients with DME. Patients have to receive multiple injections of the VEGF antibodies to maintain the visual gain. Several trails involving different combinations of treatment modalities for DME have been conducted, including laser therapy, and intravitreal injection of triamcinolone acetonide, bevacizumab, or ranibizumab. These combination therapies have proved more efficacious than monotherapy with anti-VEGF antibodies. Since the pathogenesis of DME involves multiple factors, further investigation of a combination of laser, pharmacological and surgical treatment modalities may be needed to achieve the best outcome of DME treatment.

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