Targeting the Pathophysiology of Diabetic Macular Edema

Diabetic macular edema (DME) is the leading cause of blindness in the diabetic population, and its prevalence is variable. The Diabetes Control and Complications Trial (DCCT) reported that 27% of type 1 diabetic patients developed macular edema within 9 years of diabetes onset (1). Other studies indicate that in type 2 diabetic patients the prevalence increases from 3% within 5 years of diagnosis to 28% after 20 years duration (2). DME tends to be a chronic disease, although spontaneous recovery is not uncommon. It is important to recognize that ~33–35% of patients with macular edema had spontaneous resolution after 6 months if untreated. To characterize the severity of macular edema and for treatment guidelines, the term clinically significant macular edema (CSME) as an equivalent of DME, defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS), is used.

DME is a complex disease of multifactorial origin. The common pathway that results in DME is disruption of the blood-retinal barrier (BRB). The mechanism of BRB breakdown is multifactorial and secondary to changes in the tight junctions, pericyte loss, endothelial cell loss, retinal vessel leukostasis, upregulation of vesicular transport, and increased permeability of the surface membranes of retinal vessels and retinal pigment epithelium cells. The disruption of the BRB leads to abnormal inflow of fluid into the neurosensory retina that can exceed the outflow and cause residual accumulation of fluid in the intraretinal layers of the macula.

The pathogenesis includes the existence of chronic hyperglycemia, along with the accumulation of free radicals, AGE proteins, and protein kinase C (PKC) formation, and the subsequent activation of vascular endothelial growth factors (especially VEGF-A) as well as an increase in vascular permeability. Likewise, the appearance of areas of ischemia and inflammatory factors, such as interleukin 6, also increase the synthesis of VEGF-A. All of these factors may be interrelated. For example, hypoxia and hyperglycemia upregulate VEGF-A production in diabetic retinopathy, which in turn increases vasopermeability by activating PKC. Hyperglycemia, however, can directly increase PKC and angiotensin II, both of which cause vasoconstriction and worsening of hypoxia by their effect on endothelins (3).

To treat DME, it is important to use the classification by Bresnick et al. (4) into focal or diffuse DME. This classification depends on the leakage pattern seen on the fluorescein angiogram (FA). In focal CSME, discrete points of retinal hyperfluorescence are present on the FA due to focal leakage of microaneurysms. In diffuse macular edema, areas of diffuse leakage are noted on the FA due to intraretinal leakage from a dilated retinal capillary bed and/or intraretinal microvascular abnormalities, and/or, in severe cases, from arterioles and venules, without discrete foci of leaking microaneurysms. The relevance of this classification is due to the different treatment that we can use. For focal macular edema, the laser treatment is responsive. However, in the diffuse form of macular edema, the effectiveness of photocoagulation has not been demonstrated; for this disease, a grid laser photocoagulation technique developed many years ago may reduce leakage attributable to permeability abnormalities within dilated macular capillaries with a positive effect on visual acuity and fluorescein leakage, but its use has been dropped of late due to its poor results in final visual acuity (5).

Because of the poor results obtained with laser photocoagultion in diffuse DME, alternatives to treatment based on its pathogenesis have been sought. The Diabetic Retinopathy Clinical Research Network (6) reported 2-year results of a multicenter randomized clinical trial comparing preservative-free intravitreal triamcinolone (at two concentrations: 1 mg and 4 mg) with focal/grid laser for DME. The mean visual acuity after starting the treatment was better in the laser group, although seemed to improve more rapidly in the 4-mg triamcinolone group. This study demonstrated that intravitreal injection of triamcinolone acetonide is a promising therapy for DME unresponsive to laser photocoagulation. However, the triamcinolone is an off-label treatment, and its use is not without complications. Surgical cataracts succeeded in 51%, and an increase of intraocular pressure appeared in 30% of the patients. Other steroids, such as Retisert (fluocinolone acetonide) and Porsudex (dexamethasone), are currently undergoing phase III trials.

As discussed at the beginning, VEGF-A is a major mediator of increased retinal permeability. Blockage of VEGF-A has been shown to reduce vascular permeability. Currently, we have achieved its inhibition via VEGF-A inhibitors with aptamers (pegaptanib) or antibodies targeted against VEGF-A (e.g., ranibizumab or bevacizumab). The preliminary results of the clinical trial of VEGF-A (VEGF-165 isoform) with pegaptanib has demonstrated a beneficial effect of this intravitreal drug on visual acuity and retinal thickness in a phase II trial (7), and phase III trials are underway.

Ranibizumab and bevacizumab are antibodies targeted against VEGF-A that have been widely used to treat exudative age-related macular degeneration. Bevacizumab is an off-label drug, and its use is under study. Ranibizumab is an anti-VEGF Fab fragment commonly used in the treatment of age-related macular degeneration. There are currently five multicenter, randomized phase II/III trials that aim to determine the safety and efficacy of this drug in the treatment of DME.

Massin et al. (8) demonstrated in a 12-month phase II study that the mean visual acuity improved from baseline by 10.3 ± 9.1 letters with ranibizumab and declined by 1.4 ± 14.2 with sham ($P < 0.0001$). Additionally, the proportion of patients who gained ≥ 10 letters as well as ≥ 15 letters was threefold higher in the ranibizumab arm than in the sham arm. The mean change in central retinal thickness was significantly higher in the ranibizumab arm with a decrease of 194.2 vs. $48.4 \ \mu m$ in the sham arm. There were no imbalances in the rates of ocular and nonocular adverse events between the two

arms. The most frequent ocular adverse events were conjunctival hemorrhage (22.5%), intraocular increase (20.6%), and eye pain (17.6%). A special feature of this study is the possibility of dose doubling, which was eventually undertaken in the majority of ranibizumab patients. A total of 86% of patients received a dose of 0.5 mg or higher during most of the study period, and the investigators in fact recommended a dose of 0.5 mg to replicate the efficacy.

This study appears promising for the use of the ranibizumab in the treatment of DME, with a good safety profile. Anti-VEGF drugs seem to be a promising alternative for the treatment of DME, but it is still necessary to define the dose and the time between injections. However, we must determine if they can be used as a monotherapy or in combination with other treatments, such as laser photocoagulation. A clinical trial directly comparing the efficacy and safety of anti-VEGF treatment with conventional laser therapy is warranted.

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