Diabetic Macular Edema: Towards Therapy Aimed at the Underlying Pathogenic Mechanisms

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Key words: diabetic macular edema, diabetic retinopathy, triamcinolone acetate, vascular endothelial growth factor

IMAJ 2006;8:127–128

Diabetic retinopathy is one of the leading causes of blindness worldwide. Despite the significant progress made in the treatment of diabetes mellitus in recent years, the ocular complications of this disease remain a major health challenge in developed countries as well as in the developing world, leading to visual impairment in a high percentage of affected patients [1]. The pathophysiology of diabetic retinopathy is directly related to the widespread microvascular complications of diabetes mellitus, and reduced retinal capillary blood flow occurs in diabetic patients even before any clinical signs of diabetic retinopathy develop. Retinal tissue has one of the highest metabolic rates in the body and oxygen demand is near-maximal even under normal circumstances. Thus, even mild microvascular insufficiency (compromised capillary flow) can lead to local hypoxia and ischemia. Ischemia, in turn, sets off a cascade of events, leading among other things to vascular endothelial growth factor (and possibly erythropoietin) up-regulation. VEGF, previously known as "vascular permeability factor," is one of the main causes for the two vascular processes that underlie visual impairment in diabetic retinopathy: leakage and exudation from vessels, leading to diabetic macular edema, and growth of abnormal neovessels as part of proliferative diabetic retinopathy which can lead to vitreous hemorrhages, traction retinal detachments, and neovascular glaucoma when abnormal vessels grow in the iris [2].

So where can we intervene to break this unfortunate chain of events? Primary prevention of diabetes mellitus remains an illusive goal, though it may be partially achieved through lifestyle and pharmacologic as well as possibly immunologic interventions [3]. Once these measures fail and diabetes is established, numerous large studies have shown beyond any doubt that control of blood glucose levels, as reflected by HbA1C levels, can significantly delay onset and perhaps reduce severity of the retinopathy. Despite these convincing data, a large proportion of patients fail to adequately control their diabetes; and, particularly when concomitant hypertension and dyslipdemia are present, retinopathy ensues. It is crucial to increase the awareness of patients as well as their treating physicians to the importance of controlling glucose, hypertension and dyslipidemia, as proven in the DCCT and UK-PDS studies. With the range of efficient pharmacologic agents available today to treat these risk factors, prevention and significant delaying of diabetic retinopathy onset is within reach and may be the most efficient way to reduce the visual morbidity associated with diabetes [reviewed in 4]. Moreover, even after the retinopathy develops, optimal metabolic control should continue to be the goal, and there is recent evidence that such control is associated with better response to treatment [5].

When diabetic retinopathy develops, and is associated with diabetic macular edema or proliferation of neo-vessels, the mainstay of treatment since the 1970s has been laser therapy. While the exact mechanism by which laser reduces the macular edema is still not fully understood, properly performed laser photocoagulation for clinically significant macular edema was shown to halve the rate of the progression to visual loss. Focal laser treatment is still the first line of treatment for this condition. However, it is associated with injury to the tissue (essentially causing small burns and scars in the retina and macula) and in many cases, particularly when macular edema is diffuse, is not effective. Recently, additional therapeutic modalities were introduced. One approach, applicable in those instances when vitreal traction on the macula is associated with diabetic macular edema, is to intervene surgically by vitrectomy [4]. Other approaches include a selective protein kinase C beta inhibitor (ruboxistaurin), which was demonstrated to effectively reduce visual loss in these patients, as well as a range of anti-VEGF compounds that are at different stages of clinical trials [2,6,7]. These interventions may finally be addressing the basic pathology underlying the vascular injury in diabetic retinopathy and may change the way we treat this disease in the future.

What is the role of steroids in this disorder? Any ophthalmologist in clinical practice will see a significant number of diabetic patients with vision severely affected by macular edema despite laser treatment. Many of these patients are not officially blind (blindness defined as vision worse than 6/60), but their quality of life is markedly affected because they cannot perform critically important daily activities like reading and driving. For these patients we currently do not have much in our armamentarium, and controlling the diabetes, while still important, will not bring back their sight. Intraocular and periocular steroids may be an answer for some of these patients, and the results of Barak et al. presented in this issue of *IMAJ* [8] exemplify the potential as well as the hazards of this treatment.

VEGF = vascular endothelial growth factor

Intraocular and periocular triamcinolone acetate injections have gained considerable popularity in recent years, even though large, prospective well-controlled trials are only now beginning to emerge. The availability and low price of this compound, combined with the sometimes magical effects of steroids, have contributed to its growing use. In addition, the possibility to apply it locally to the eye markedly lessens the systemic side effects usually associated with steroids. Thus, triamcinolone acetate (and other steroid preparations) have been applied with variable success in many retinal conditions, such as macular degeneration, central and branch retinal vein occlusions, and posterior uveitis [9]. In diabetic retinopathy, while it does not address the primary problem of microvascular perfusion, triamcinolone acetate was shown to effectively reduce the secondary destructive process related to swelling, exudation and neovascularization. Steroids modulate VEGF action at multiple levels, and apparently have anti-angiogenic as well as anti-permeability effects. The dramatic effect that triamcinolone acetate injection can sometimes have on diabetic macular edema is easily demonstrated with optical coherence tomography. Looking at the magical disappearance of macular edema on OCT 1 week after intravitreal triamcinolone acetate injection is nothing less than spectacular. However, there is often a price to pay for this magic. For one, the basic pathology of capillary non-perfusion is not dealt with, and if the primary reason for poor vision is macular ischemia and not the edema per se, the dramatic structural improvement is not accompanied by any functional visual change. Secondly, in the presence of a significant vitreo-retinal interface abnormality, such as taut posterior hyaloid, the swelling will probably not subside without surgical intervention. Thirdly, the injection may be associated with significant iatrogenic damage, including cataract progression in the majority of phakic patients, intraocular pressure elevation (which occurs in over 30% of cases); and, rarely, the devastating complication of intraocular infection (endophthalmitis) may occur [9]. Most of these complications are treatable, but in a diabetic patient with multiple health problems, even a treatable condition may become challenging. Last but not least, the effect of intravitreal triamcinolone acetate injection, though dramatic, in the majority of cases is only temporary and will usually subside within 3 to 6 months. At that point, one is faced with the dilemma whether to inject again and how often. The long-term effects and the impact of repeated injections have not yet been properly evaluated in the literature.

The article by Barak and colleagues [8] shows that in certain patients with diffuse macular edema a short-term improvement in visual acuity may indeed be achieved using intravitreal triamcinolone acetate injections. The study also highlights some of the risks associated with this type of therapy. While longer term studies combined with quantification of the macular edema by OCT retinal thickness measurements would be helpful, this study is important in that it helps to guide us to the way that triamcinolone acetate injections should be perceived and used. It is quite clear that intravitreal triamcinolone acetate injections are not and will not become a panacea for retinal edema. However, there may be a role for this treatment as a temporizing measure in a well-chosen subset of diabetic patients who should fill the following criteria:

- Presence of typical cystoid macular edema
- No significant macular ischemia
- No vitreo-retinal interface abnormalities
- No history of glaucoma or elevated intraocular pressure
- Willingness to accept the risk of the common complications
- If not yet performed, focal and/or grid laser should be applied as required
- Willingness to systemically control the diabetes and the associated risk factors.

The last two criteria, in our opinion, are extremely important, because in diabetic patients any short-term intervention should be accompanied by a long-term strategy; otherwise, it is doomed to fail. In the near future we will probably see an attempt to replace and augment intraocular injections of triamcinolone acetate with more specific intravitreal anti-VEGF therapies. A recent article demonstrated the positive effect of such treatment using the anti-VEGF aptamer pegaptanib [7], and more mechanism-directed treatment modalities are in the pipeline. Time will tell if these new interventions allow better control and lessen the impact of macular edema on vision and quality of life of diabetic patients.

OCT = optical coherence tomography

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