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Optimal current and future treatments for diabetic macular oedema

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Abstract

Diabetic retinopathy is the most common cause of vision loss in working-age adults. Both inflammation and vascular endothelial growth factor (VEGF) play a critical role, modern and emerging treatments have centred on both laser photocoagulation and new pharmacologic strategies to improve the prognosis. Focal and grid photocoagulation, as described in the ETDRS trials, remain the gold standard of treatment. New classes of agents include long-acting steroid formulations delivered as intravitreal injections and also anti-VEGF agents. In addition, studies are under way to evaluate potential benefits from other novel agents, including those acting on the mammalian target of rapamycin pathway. In limited numbers of direct head-to-head comparisons, both steroids and anti-VEGF agents appear to be superior to conventional photocoagulation in reducing macular oedema in the first 4–6 months after treatment, although laser photocoagulation appears to be superior at time points of 1–2 years. In addition, there appear to be significant potential long-term complications of steroids including cataracts and glaucoma that may limit their use in certain patients. New methods of the laser delivery including shorter pulse durations and pattern scanning may also improve the effectiveness and risk profile of laser from the patient prospective. Finally, multi-modality therapy may play an increasingly important role.
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Introduction

Diabetes mellitus, through its ophthalmologic complications, principally diabetic retinopathy, is the leading cause of vision loss and blindness in working-age adults in industrialized nations including the UK and the Unites States. It is estimated that as of 2002 there were approximately 13.5 million diabetic patients in the United States, constituting in excess of 6% of the population and more than 14% of adults over the age of 65. Of the 10.2 million US adults aged 40 and older known to have diabetes mellitus, prevalence rates for retinopathy and vision threatening retinopathy are reported to be 40.3% and 8.2%, respectively, corresponding to in excess of 900 000 persons currently under active treatment in the US. The 10-year incidence of moderate vision impairment requiring treatment is thought to range from 21.4% for older onset diabetics not taking insulin to 32.8% of older onset patients using insulin. Unfortunately, although there are significant advancements being made in the early diagnosis and treatment of patients, the number of patients at risk for the development of vision loss or blindness due to diabetic retinopathy is still thought to be increasing since the worldwide incidence of diabetes, principally as the result of changing dietary habits in countries that are undergoing rapid industrialization, as well as increasing obesity in established industrialized nations. Some estimates have projected that by the year 2050, there will be 50 million or more diagnosed and undiagnosed diabetic patients in the United States, of whom as many as half or 25 million may have diabetic retinopathy unless major changes in nutritional status and disease prevalence occur.[1,2]

The two principal forms of diabetic retinopathy are non-proliferative disease and proliferative disease, of which the latter is less common, but results in more severe loss of vision, particularly in insulin-dependent diabetics. Clinically significant diabetic macular oedema, a severe form of non-proliferative disease, results from extracellular swelling,

particularly in Henle's layer in the macula, as well as intra- and extracellular oedema from breakdown of the blood–retinal barriers with resulting dysfunction in the retinal photoreceptors. The onset and severity of clinically significant macular oedema, the principal subject of this discussion, are known to be related to the duration and severity of diabetes, with patients manifesting poor levels of glycemic control as evidenced by high haemoglobin A1C concentrations, at much greater risk for disease than those with better levels of control as shown in a number of prospective randomized clinical trials.[3] Although the precise linkages between poor diabetic control and diabetic retinopathy remain incompletely understood, there is mounting evidence that the development of advanced glycation end products and activation of a variety of intermediate inflammatory mediators and cytokines, including ICAM-1 and vascular endothelial growth factor (VEGF), as well as TNF-α and interleukins all have important early roles.[4–8] The activation of these cytokines and their receptor interactions result in secondary intracellular messaging, of a number of pathways including hypoxia inducible factor 1A (HIF1α), various tyrosine kinases including protein kinase C (PKC), mammalian target of rapamycin (mTOR), nitric oxide synthetase, and Src kinases. As a result, from a pharmacologic perspective, there are many potential points of attack to interrupt the pathways ultimately leading to increased cellular permeability and macular swelling.[4,5,7,8] Other approaches including laser photocoagulation have been shown to be effective for many decades, in addition to recent approaches to treatment, including removal of the retinal internal limiting membrane and vitrectomy.[9,10] As of the present, the two principal non-surgical categories of treatment for diabetic retinopathy are (1) retinal laser photocoagulation, and (2) pharmacologic approaches. In a select subset of patients, vitreous surgery may be of benefit when there is evidence of abnormal vitreomacular adherence, but as of yet, there is insufficient level-one evidence to suggest that primary vitrectomy with or without membrane peeling in patients with uncomplicated diabetic macular oedema is as effective as either laser photocoagulation or other retinal pharmacologic methods of treatment. As a result this review focuses on the first two non-surgical categories.

Laser photocoagulation

Retinal laser photocoagulation is presently thought to be the most cost-effective method of treatment for most patients with both diabetic macular oedema and proliferative diabetic retinopathy, based on the results of a large number of well-controlled prospective randomized trials dating back to the early 1970s. In the landmark ETDRS, 2244 patients with clinically significant macular oedema were randomized to either early treatment with focal and grid photocoagulation, or deferral of treatment and followed with careful fundus photography and masked standardized visual acuity measurements. Within 1 year of randomization, approximately 5% of laser-treated patients and 8% of control patients had lost three lines or more of vision and by 3 years moderately severe vision loss in the untreated group had increased to 12% in the laser group compared with 24% in the deferral group.[9] Increased clinical experience and more liberal use of grid photocoagulation in addition to focal microaneurysm closure techniques caused some physicians to question whether macular grid photocoagulation was as or even more effective than focal photocoagulation in treating patients with clinically significant diabetic macular oedema. The use of grid photocoagulation alone in a pattern, termed mild macular grid technique, was compared to the modified ETDRS treatment, which consisted of both focal closure of aneurysms and applications of light grid photocoagulation, to oedematous areas as part of the Diabetic Retinopathy Clinical Research Network collaborative approach (DRCR). Although both techniques were shown to reduce macular oedema and improve the visual prognosis in patients with diabetic retinopathy, particularly when compared with the natural history, the modified ETDRS treatment incorporating both focal and grid methods was judged to be somewhat superior to modified grid photocoagulation alone in improving vision and reducing macular thickness as measured by OCT examination.[10] Recently, the DRCR compared the relative effectiveness of modified ETDRS laser treatment alone in patients with clinically significant macular oedema with either a low dose (1 mg), or a high dose (4 mg) of intravitreal triamcinolone in a prospective randomized trial involving 840 patients. In this study, although there appeared to be earlier improvements in patients receiving 1 or 4 mg of triamcinolone at 4 months after treatment, compared with laser by 12 months, laser-treated patients appeared to have better visual acuity and greater reductions in OCT-measured macular thickness compared with either steroid group, differences that were only further magnified at 24 months.[11]

Although conventional laser photocoagulation has stood the test of time as a cost-effective treatment, new developments in laser systems may result in even more advantageous outcomes in terms of both efficacy and tolerance in the future. The development of pattern scanning lasers has improved the precision and efficiency of macular laser photocoagulation and

pan-retinal photocoagulation compared with conventional longer-duration single-spot photocoagulation.[12] Experimental studies in both pre-clinical animal models and OCT studies in humans suggest that when pulse durations of 10–20 ms are used rather than conventional 100 ms applications, there is less damage to the entire thickness of the retina, with lesions spatially confined to the outer one-third with consequent preservation of the nerve fibre layer and ganglion cell layers. This may result in fewer secondary complications including loss of visual field and other psychophysical parameters associated with function of second- and third-order retinal neurons, which are typically preserved.[13,14] It has been established that shorter pulse duration burns have a resultant smaller diameter footprint on the retina, both laterally and axially, than longer duration burns with calculated axial retinal injury of 70 μm for 10 ms burns contrasted with approximately 220 μm for a 100 ms burn.[13] Fundus auto fluorescence and Fourier-domain optical coherence tomography in patients undergoing diabetic laser photocoagulation with 10 and 20 ms patterned short-duration burns suggest that gradual retinal lesion enlargement or 'creep' does not occur with shorter burns and that there may actually be progressive shrinkage rather than enlargement of these burns over time. There may also be preservation and/or remodelling of the outer retinal layers including filling in of initial defects in photoreceptors, presumably by sliding from adjacent areas in pre-clinical models for smaller-sized burns of 200 μm or less, that may favourably affect VEGF distribution in the retina and visual field loss.[14–16] Clinical photocoagulators that combine fluorescein angiography with image stabilization and tracking have recently been introduced to facilitate more efficient focal photocoagulation and delineation of zones most appropriate for treatment (personal communication, Navilas, 2009). New automated photocoagulation regimens to programmed photocoagulation of perimacular regions with grid photocoagulation linked to corresponding OCT thickness maps have also recently been developed and are undergoing clinical evaluation (personal communication, D Palanker, Stanford University, OptiMedica Corporation, Santa Clara, CA, USA, 2009).

Retinal pharmacologic therapy

Steroids

Initially, uncontrolled pilot studies, and recently, a variety of prospective randomized clinical trials have shown a useful role for intravitreal steroids in the treatment of diabetic macular oedema.[17–21] The mechanism of action is thought to be complex, but presumably is related to a variety of points of interaction, including lysomal stabilization, inhibition of ICAM and TNF pathways, and anti-VEGF effects.[4–8] In the largest prospective randomized trial of triamcinolone performed to date, by 4 months after administration of 4 mg triamcinolone, average visual acuity improved compared with either 1 mg intravitreal triamcinolone or focal modified ETDRS treatment photocoagulation.[11] However, this improvement was not sustained over time, possibly due, in part, to the development of tachyphylaxis and intercurrent complications including cataract and elevated intraocular pressures, such that by 12 months the average visual acuity in patients receiving 4 mg triamcinolone was reduced compared with baseline or laser photocoagulation. By 2 years, even with re-treatment with triamcinolone allowed, in patients receiving 4 mg triamcinolone, average change in visual acuity was a loss of three letters contrasted with the loss of two letters for the patients receiving 1 mg of drug, and an average gain of one letter for patients receiving photocoagulation.[11]

Sustained delivery steroid formulations

A number of both bioerodable and non-bioerodable polymeric systems have been developed to achieve sustained levels of steroids into the vitreous cavity for the treatment of a variety of retinal vascular indications including diabetic macular oedema.[20–23] In one such study using dexamethasone impregnated into a co-polymer of polylactic glycolic acid, patients receiving either 700 μg of sustained delivery dexamethasone or 350 μg of a similar formulation achieved a 10-letter or more improvement in best corrected visual acuity at 90 days in 33.3 and 21.1% of patients respectively compared with 12.3% of untreated controls ($P < 0.007$). There are comparable rates of improvement in 30% and 19% *vs* 23% in the observation group at 180 days. These results were paralleled by reduced macular OCT thickness measurements in the treated patients compared with the untreated controls. In this study consisting of 171 patients with 57 in each treatment group, complications specific to steroids including elevated intraocular pressure and cataract were significantly lower than historical complication rates for either conventional triamcinolone or sustained delivery of fluocinolone. By day 180, there were no statistically significant differences in the number of reported cataracts between any of the study groups and no cases of either retinal detachment or endophthalmitis in any group. Approximately 15% of eyes in the 700 and the 350 μg dexamethasone groups sustained transient intraocular pressure increases relative to baseline at some point through day 180 contrasted with only 2% in the observation group. All such patients were able

to be well controlled with topical oculohypotensive medications and no patients required filtration surgery in this study.[21]

In a prospective randomized clinical trial conducted by Bausch & Lomb in which fluocinolone was placed within a non-bioerodable reservoir implanted in the eye, 27.6% of patients receiving 0.59 mg drug compared with 14.5% of those receiving standard of care achieved three lines or greater of visual acuity improvement at 3 years ($P<0.05$, $N=196$ patients). However, the majority of the phakic patients in this study required cataract extraction, and the majority of patients in the drug group contrasted with 19.6% in the standard of care group (nearly 40%) required treatment (personal communication, B Kuppermann, 2009). As a result, the Retisert implant, which has been approved for the treatment of severe forms of intractable uveitis, has not received the FDA clearance in the United States for the treatment of diabetic macular oedema.[22] A newer generation, smaller, non-bioerodable polymer-containing lower doses of fluocinolone (Iluvien; Alimera Sciences, Alpharetta, GA, USA) showed in preliminary 18-month interim data analysis, that 36% of patients receiving 0.45 μg daily fluocinolone acetonide achieved best corrected visual acuity improvement of 15 or more letters, 18 months after administration. Final results of the study remain unknown at the time of the writing this paper[23] (personal communication; Alimera, 22 October 2009). Additional studies are also under way including the use of a helical surface-coated intravitreal triamcinolone implant able to be screwed into the vitreous cavity through a subconjunctival transcleral approach and removed more expeditiously than other non-bioerodable devices according to the study sponsor (personal communications, Surmodics Inc., June 4, 2009).

VEGF inhibitors

Because of its central role in the pathogenesis of both proliferative diabetic retinopathy and diabetic macular oedema, molecules designed to inactivate extracellular VEGF have been explored as potential treatments for diabetic macular oedema.[24–28] In one phase 2 randomized double-masked clinical trial, pegaptanib (Macugen) the first aptameric anti-VEGF inhibitor approved for human use, produced improvement in median visual acuity at week 36 with 0.3 mg of drug compared with sham control. In addition, 34% of patients gained two or more lines of vision contrasted with 10% of controls, and mean central thickness decreased in treated patients by 68 compared with 4 μm in sham-treated patients.[26]

In one prospective randomized clinical trial, patients with refractory diabetic macular oedema were randomized to one of three arms, sham injection, intravitreal bevacizumab (Avastin) 1.25 mg, or combined intravitreal bevacizumab 1.25 mg and intravitreal triamcinolone 2.0 mg, three injections of bevacizumab in both drug groups. A total of 115 eyes of 101 patients were enrolled. Central macular thickness was reduced by 95.7 and 92.1 μm in the monotherapy and combined drug groups, respectively, and only 34.9 μm in the control group at 24 weeks. At the same time point visual acuity improvements to a statistically significant degree were seen in both the monotherapy and the combined therapy groups compared with sham treatment, and elevation of intraocular pressure in only 8.1% of the combined group.[27] In another study, patients receiving either 1.25 or 2.5 mg bevacizumab showed an OCT-measured reduction in central macular thickness of more than 11% in 43% of treated eyes compared with 28% treated with laser alone at 3 weeks, although by 6 weeks laser treated eyes were more likely to show reduction (50%) than bevacizumab-treated eyes (37%).[25] Although the results for bevacizumab for diabetic macular oedema are modest at best, and the drug is not yet approved for ophthalmologic use, intravitreal injection of bevacizumab has become part of the standard of care in many centres in the United States and the UK in conjunction with photocoagulation and intravitreal steroids.[19,24]

Ranibizumab (Lucentis), which has been approved for intravitreal injections in humans for age-related macular degeneration, has similarly been investigated as a potential therapeutic agent in the treatment of diabetic macular oedema. In one recently published study, 126 patients with diabetic macular oedema were randomized 1 : 1 : 1 to receive 0.5 mg ranibizumab at baseline and at months 1, 3, and 5, or focal grid photocoagulation at baseline and month 3, if needed, or a combination of both, at months 1 and 3. Six months after initiation of therapy, the mean gain and best corrected visual acuity were greater in patients receiving three consecutive injections of ranibizumab than either the group receiving focal modified ETDRS grid photocoagulation at baseline and at month 3, or a single injection of ranibizumab at baseline and photocoagulation at month 3. Excess focal thickness was reduced in all three groups with no significant differences between the three.[28] These results are similar in general character to the short-term results seen with intravitreal triamcinolone compared with laser photocoagulation. Until comparable data are obtained for years 1 and 2, no definitive recommendations can be made about the advisability of ranibizumab compared to photocoagulation or, for that matter, intravitreal steroids without a direct comparison. Phase 3 studies are currently under way to evaluate these issues, and it is

anticipated that this data should be available within the next several years.

PKC inhibitors

Because the PKC pathway is known to be an important intracellular signalling mechanism following activation of VEGF receptors, and because pre-clinical studies in animal models suggested that PKC inhibitors slowed the rate of diabetic retinopathy progression, a large prospective randomized clinical trial was conducted comparing the rate of progression of diabetic retinopathy between patients receiving standard of care and those receiving an oral administration of a proprietary PKC inhibitor (ruboxistaurin). In this study, 685 patients were randomized to receive either oral ruboxistaurin (32 mg per day), or placebo. Sustained moderate visual loss occurred in 9.1% of placebo-treated patients compared with 5.5% of ruboxistaurin-treated patients (40% risk reduction, $P<0.04$) with mean visual acuity slightly improved in the ruboxistaurin-treated group compared with placebo-treated group, and a reduced likelihood of laser photocoagulation compared with placebo-treated controls. However, because the absolute magnitude of the effect was relatively modest, the drug did not receive approval for human use by the FDA, and it is currently not in common clinical practice in the United States or elsewhere.[29]

mTOR inhibitors

Sirolimus (rapamycin) is a naturally occurring macrolide, which forms a complex with the immunophilin FK binding protein 12 and inhibits the mTOR pathway, which is a convergence point for multiple intracellular regulatory pathways. Because inhibition of mTOR inhibits VEGF signaling through downregulation of HIF1α, it results in an indirect inhibition of VEGF effects, as well as other immunomodulatory effects. In a recent phase 1 pilot study (oral communication, P Dugel, MacuSight, 2008), both intravitreal and subconjunctival injections of a sustained release formulation of Sirolimus appeared to be well tolerated and resulted in apparent reduction in diabetic macular oedema and visual acuity improvement in selected patients. For a small group of patients in the subconjunctival group, median visual acuity began to improve at day 7 (5.0 letters), and remained at four letters by day 90. Somewhat less notable changes were seen in the intravitreal group at day 90 as well with a median increase in visual acuity of two letters and a median reduction in retinal thickness of 52 μm at day 45.[30] A phase 2 study in a larger cohort of patients has been completed but as yet no data are available for that group and as a result no definitive recommendation can be made regarding the long-term safety and efficacy of this therapy, which at present is not approved for human use.

Conclusions

Diabetic macular oedema remains an important but treatable complication of diabetes mellitus at the present time with nearly one million affected persons in the United States alone, and a likely increase projected over time due to the increasing prevalence of diabetes mellitus in the population anticipated over the next 40 years. Laser photocoagulation is a proven cost-effective form of therapy more than four decades after its introduction. Over the long-term, the relative advantages and disadvantages of laser photocoagulation compared with modern pharmacologic therapies, such as low dose, sustained delivery preparations of steroids, VEGF inhibitors, mTOR inhibitors, or other classes of pharmacologic agents, remain unknown, but are currently under active study. Pharmacologic studies appear to suggest that although intravitreal injection may produce a more rapid reduction in central macular thickness and improvement in visual acuity for periods of up to 3–6 months after initial administration, these results are not permanent and require repeated re-injection, at least until such time as safe and effective sustained delivery formulations are available. In addition, the long-term complications associated with certain intravitreal pharmacologic agents such as high-dose fluocinolone acetonide reservoir systems and triamcinolone, including cataract and glaucoma, may limit their effectiveness over the long-term even if short-term benefits are apparent at 4 months. There appears to be considerable opportunity for improvement of existing pharmacologic agents through the use of lower doses and sustained delivery systems, but as yet definitive solutions have not been proven through well-controlled prospective randomized studies, although a number of such studies are currently under way and enrolling patients. Similarly, the potential benefits of multi-modality therapy including different classes of pharmacologic agents combined with one another, as well as the combination of various classes of pharmacologic agents either alone or in combination with photocoagulation, remain intriguing and worthy of additional study.

Finally, the potential for interventions, such as either surgical or pharmacologic removal of vitreal traction, or surgical removal of the internal limiting membrane, is also an intriguing approach, although beyond the scope of this review. The development of new and improved laser delivery systems, including machines with the capability to delivery patterns, shorter pulse durations ranging

from microseconds to 10–20 milliseconds, and image guidance and tracking, may also provide opportunities for further improvement in treatment outcomes for diabetic macular oedema.

Conflict of interest

The author is a consultant to OptiMedica Corporation, which manufactures lasers used in the treatment of diabetic retinopathy, as well as Allergan, Genentech, Macusight Pharmaceuticals, and Lilly, which are investigating the use of long-acting formulations of steroids, ranibizumab, Sirolimus, and ruboxistaurin for its treatment.

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