Role of Steroids in the Management of Diabetic Macular Edema and Proliferative Diabetic Retinopathy

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Role of Steroids in the Management of Diabetic Macular Edema and Proliferative Diabetic Retinopathy

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ABSTRACT

Diabetic retinopathy is the most common microvascular complication of diabetes. Early clinical trials have established the efficacy and safety of laser in the treatment of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Despite timely and appropriate use of laser, some patients continue to experience visual loss. The pathogenesis of PDR and DME is multifactorial involving both angiogenic and inflammatory processes. Recent trials have shown that the anti-inflammatory and anti-angiogenic properties of corticosteroids may provide benefit in treating PDR and DME. The exact role of steroids in the treatment for diabetic retinopathy and macular edema remains to be fully elucidated.

Keywords: diabetic retinopathy; diabetic macular edema; corticosteroids; triamcinolone acetonide

Diabetes mellitus (DM) will affect over 366 million individuals worldwide by 2030. The Centers for Disease Control estimates that 23.6 million individuals, representing 7.8% of the entire U.S. population, have DM and that an additional 57 million have pre-diabetes. The ocular complications are the most frequently occurring of the diabetic microvascular complications and diabetic retinopathy (DR) is ultimately present in nearly all patients with DM. In the past 20 years, DR has remained the leading cause of new onset blindness in the adult population aged 20–74 years in United States (US) and other industrialized nations.

Proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) are the primary causes of visual loss in diabetic patients. Panretinal photocoagulation (PRP) as treatment for PDR was first introduced over 40 years ago. The safety and effectiveness of PRP has been validated by many studies, including the Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS). With appropriate and timely treatment, the risk of severe visual loss due to PDR can be reduced to less than 5%. PRP is the only established treatment modality for PDR proven to consistently induce long-term quiescence and prevent further visual loss in diabetic patients with PDR.

In contrast, standard treatment for DME is somewhat less effective and more variable in outcome. DME can be present at any stage of DR and is the leading cause of moderate visual loss, afflicting nearly 1.2 million individuals in the US alone. DME is more common in Type 2 DM patients on insulin than Type 1 DM patients, and prevalence increases in both DM types as the duration of diabetes increases. The natural course of untreated DME is characterized by chronic continued retinal vascular leakage and retinal thickening, often with intraretinal lipid deposition. The use of focal laser photocoagulation as the standard of care treatment of DME was established over 20 years ago.
by the findings of the ETDRS and still remains the standard to which novel treatments are compared.\textsuperscript{11,12} The ETDRS demonstrated that focal/grid laser photocoagulation effectively reduces the risk of moderate visual loss (doubling of the visual angle) by 50\% in 3 years.\textsuperscript{11} The ETDRS utilized a clinical definition of DME, and showed that 24\% of eyes with clinically significant macular edema (CSME) and 33\% with center involving CSME will have moderate visual loss (MVL) within 3 years if left untreated.\textsuperscript{11} More recent studies, as well as re-evaluation of the ETDRS data, have suggested that involvement in particular of the center of the macula may be more important in determining visual outcome.\textsuperscript{13–15} Thus, current studies now primarily stress center involvement rather than CSME per se.\textsuperscript{13,14} Investigations to determine if the quantity and pattern of lipid exudates and source of fluorescein leakage may aid in assessment are also underway.\textsuperscript{14}

The development of macular edema in diabetes is multifactorial but at least in part involves a breakdown of the blood-retinal barrier (BRB), eventually leading to photoreceptor dysfunction.\textsuperscript{16} Systemic alterations in metabolic control, uncontrolled hypertension, and other systemic risk factors (renal disease, anemia, dyslipidemia) contribute to the continued breakdown of the BRB causing prolonged extravascular leakage and macular edema.\textsuperscript{17} An increased permeability of retinal capillaries and microaneurysms results in the accumulation of extracellular fluid and thickening of the macula.

The breakdown of the BRB may result from a dysfunction of intercellular junctions, increased transcellular transport, or increased endothelial cell destruction.\textsuperscript{18,19} Inflammatory mediated disruption of intercellular junctions and vascular permeability may also play a role in the development of DME. Inflammatory mediators increase vascular permeability by binding to specific receptors that transduce intercellular signals, which in turn cause cytoskeletal reorganization and widening of the interendothelial clefts.\textsuperscript{18,20} Inflammatory mechanisms promote leukostasis within retinal capillaries.\textsuperscript{21} The metabolic changes in diabetes lead to an increased expression of leukocyte adhesion molecules causing an increased propensity of activated leukocytes to adhere to the retinal vascular endothelium.\textsuperscript{22} Fas-mediated endothelial cell apoptosis may promote further breakdown of the BRB.\textsuperscript{23} This breakdown may be enhanced by angiogenic and vascular permeability factors such as VEGF,\textsuperscript{24} protein kinase C activation,\textsuperscript{25} and advanced glycation end products.\textsuperscript{26,27} Finally, mechanical factors such as vitreoretinal traction and posterior vitreous anomalies may also contribute to the continued disruption of the BRB.\textsuperscript{10} Since the seminal work by Gordon and McLean, corticosteroids have gained widespread use in ophthalmology.\textsuperscript{28} Corticosteroids have been primarily used in treatment of inflammatory disorders.\textsuperscript{29} However, angiostatic properties of corticosteroid have also been identified\textsuperscript{30} with subsequent focus on potential therapeutic roles in neovascular and exudative diseases.\textsuperscript{31}

Folkman and colleagues in 1983 were the first to describe angiogenesis inhibition by heparin or a heparin fragment administered with cortisone.\textsuperscript{30,32} This new class of “angiostatic steroids” had promising clinical applications as the angiostatic function was found to be independent of either glucocorticoid or mineralocorticoid activity.\textsuperscript{33} Tetrahydrocortisol, a metabolite of cortisol, is the most potent known naturally occurring angiostatic steroid.\textsuperscript{32,33} Dexamethasone has glucocorticoid (anti-inflammatory) activity that is 25 times more potent than cortisol but with little or no angiostatic activity.\textsuperscript{34} The mechanism of action of these steroids depends on their ability to specifically alter basement membrane turnover in growing capillary blood vessels.\textsuperscript{33,34} These steroids represent a prototype of angiogenesis inhibitors with potential therapeutic use as adjunctive treatments in diseases dominated by abnormal neovascularization.\textsuperscript{34}

Based on the work of Folkman and colleagues, a new class of angiostatic cortisones were developed which had broad angiostatic activity but were devoid of conventional glucocorticoid activity.\textsuperscript{35} The prototype drug, anecortave acetate (Retaane, Alcon Laboratories), was evaluated in clinical trials for neovascular age-related macular degeneration (AMD). Initial trials demonstrated that anecortave acetate had greater benefit than placebo and an effect comparable to photodynamic therapy in preventing visual loss.\textsuperscript{36,37} However, further development of anecortave acetate for the treatment of neovascular AMD was terminated by the manufacturer Alcon Laboratories after a planned interim analysis of trial data from 2,546 patients was completed showing that anecortave acetate had no effect on the primary or secondary endpoints at 24 months.\textsuperscript{38} Additionally, two initial open-label phase 1 trials of anecortave acetate for diabetic retinopathy\textsuperscript{39} and rubecosis iridis\textsuperscript{40} were terminated before study completion.

The broad biologic activity and multiple pharmacologic effects of corticosteroids supported the rationale behind its use for treatment of DME. Corticosteroids have been found to inhibit both VEGF and VEGF gene expression.\textsuperscript{19,25,41} Its anti-inflammatory activity in part relies on blocking the release of arachidonic acid from cell membrane and reducing the synthesis of inflammatory prostaglandins.\textsuperscript{16,21} It has also been shown to
inhibit the migration of leukocytes and stabilize the endothelial cell tight junctions.22

Following the first initial reports by Jonas42 and Martidis,43 the treatment of DME with intravitreal triamcinolone acetonide (IVT) gained widespread use. The initial case series and small, uncontrolled randomized clinical trials observed a rapid and often dramatic reduction in macular thickness and improvement in visual acuity.44-47 This effect was transient and required repeated injections which were associated with an increased rate of steroid related complications such as cataract progression and elevation of intraocular pressure.

Massin et al. initially described a small, prospective 6-month clinical trial of a single 4 mg IVT injection for diffuse DME unresponsive to focal/grid laser treatment.46,48 Treatment with 4 mg IVT reduced macular thickness at 1 (IVT 228, Uninjected 501 µm; p < 0.001) and 3 months (211, 444 µm; p < 0.001). However, no difference was observed in macular thickness in IVT injected eyes compared to uninjected eyes at 6 months (358, 441 µm; p > 0.1). IVT injected eyes were observed to have gained more ETDRS letters at 1(IVT 7.1 Uninjected -1 letters; p 0.005), 3 (9.7, -2.8 letters; p 0.002) and 6 months (6.9, -2.6 letters; p 0.013), but at 7 months the visual benefit from IVT was no longer significant (p = 0.17). All study eyes had previously received and were unresponsive to focal/grid laser treatment prior to participation in the study. The study did not employ a laser control arm; consequently, the benefit observed cannot be directly compared to laser. The authors advocated long-term trials with repeated injections to affirm the visual benefit.46,48

Gillies et al. was the first to report on the 2-year results of a double masked, placebo-controlled randomized clinical trial of 4 mg IVT in eyes with DME and impaired vision that persisted or recurred after laser treatment. Over the study period, it was shown that IVT treatment substantially reduced the need for further laser treatment (p = 0.0001). A mean improvement of 5.7 ETDRS letters, and an overall shift towards greater visual gain in IVT treated eyes (p = 0.013), was observed in IVT treated eyes compared to placebo. Furthermore, foveal thickness in IVT treated eyes had decreased by 59 µm more than in eyes treated with placebo (p = 0.009). This study showed that in eyes with center involved DME unresponsive to focal laser treatment, repeated IVT treatment improved vision and reduced macular thickness over a two-year period as compared to no treatment.47 Once again, there was no laser control arm in this study. An improvement of 5 letters or more in 26% of placebo and 56% IVT treated eyes led the authors to conclude that spontaneous improvement, similar to what was observed with the original ETDRS control arm, could still occur in eyes that have been severely affected by DME.11,47

Ockrim et al. conducted a moderately sized, randomized trial comparing the one-year best corrected visual acuity (BCVA) and macular thickness outcomes of focal laser to 4 mg IVT in patients with persistent DME.45 It was observed that the IVT treated group had a greater reduction in macular thickness (IVT 82 µm, laser 62.3 µm), but this difference did not reach statistical significance (p = 0.738), and one-year BCVA (ETDRS letters 54.4, 54.7 p = 0.44) was no different from the focal laser treated group.45

The potential clinical importance of corticosteroids in the treatment of diabetic macular edema was recognized by the National Eye Institute supported Diabetic Clinical Research Network (DRCR.net), which conducted two steroid related prospective randomized clinical trials. The initial DRCR.net trial evaluated both anterior and posterior subtenon injections of triamcinolone acetonide and did not show any benefit for the treatment of DME in eyes with either normal or slightly reduced visual acuity.49 An earlier smaller randomized trial in patients having worse visual acuity compared to the population in the DRCR.net trial, showed equivocal results.50 Due these findings, pursuit of a larger phase III trial of peribulbar or subtenon steroids for DME was abandoned.49

The second DRCR.net trial evaluated the efficacy and safety of IVT compared to focal/grid photocoagulation using a prospective multicenter randomized design. A meta-analysis of earlier randomized controlled trials had shown IVT to have significant short-term benefit in the treatment of DME.44 The DRCR.net conducted a 2-year, multicenter, randomized, laser controlled study of intraocular preservative free triamcinolone acetonide.12 Eight hundred forty eyes with center-involving DME and reduced VA of 20/40 to 20/320 were enrolled.12 The study had three treatment arms and eyes were randomized either to focal/grid photocoagulation (n = 330), 1 mg IVT (n = 256) or 4 mg IVT (n = 254) with retreatment for new or persistent DME performed at 4 month intervals and the primary outcome measured at 2 years.12 At 4 months, it was observed that both 1mg IVT and 4 mg IVT treated eyes had greater improvement in BCVA (ETDRS letters corrected for baseline differences in VA and prior laser; 4 mg, 3.8; 1 mg, 3.6) as compared to focal/grid photocoagulation (p = <0.001, 0.001).12

However, by 1 year there were no significant differences in BCVA between the three groups.12 Beginning at 16 months and extending to the primary outcome at 2 years, the laser group had a greater improvement in BCVA (mean change in ETDRS letters 1 ± 17) than
the IVT groups, both of which showed a loss of ET-DRS letters (4 mg $-3 \pm 22$ p = 0.02; 1 mg $-2 \pm 18$ p = 0.002) and were not statistically different from each other (p = 0.49). Limiting the analysis to eyes that were pseudophakic at baseline or had no or limited cataract at 2 years did not change the results. Furthermore, there was no evidence of substantially different results in subgroups based on baseline visual acuity, baseline macular thickness, or prior focal/grid photocoagulation for DME.

The effect on macular thickness was generally similar to that of visual acuity; the 4 mg IVT group achieved an initial rapid dramatic reduction in macular thickness at 4 months (mean change $-98 \, \mu m$) compared to laser ($-39 \, \mu m$, p = 0.01) and 1 mg IVT ($-16 \, \mu m$, p < 0.001). At 2 years, as observed in the visual acuity findings, the trend reversed and the laser group had a greater reduction in macular thickness ($-139 \, \mu m$) compared to the 1 mg ($-86 \, \mu m$ p < 0.001) and 4 mg IVT ($-77 \, \mu m$ p < 0.001) groups with no statistical difference between the two IVT groups (p = 0.91). The larger reduction in macular thickness in the laser treated group was present regardless of the degree of retinal thickening at baseline.

The visual outcome in all three treatment groups appeared to be better than the untreated natural course, although this was not evaluated specifically in this study. However, there was a nearly four-fold increase in both the rate of intraocular pressure elevation (p < 0.001) and the need for cataract surgery (p < 0.001) in the steroid treatment groups.

The DRCR.net trial results highlight the need for incorporation of a laser arm as the current standard-of-care for interventional trials evaluating novel therapies. The role of intravitreally administered corticosteroids as an adjunct therapy in treatment of DME or for cases in which laser has failed over the long term remains to be evaluated by ongoing studies.

Future clinical trials evaluating the efficacy and safety of corticosteroids should utilize visual acuity as the primary outcome measure since, although visual acuity and retinal thickness are correlated, there is substantial variability and vision may improve despite increased thickening or worsen with reduced thickening. Studies have clearly demonstrated that OCT-measured reduction of macular thickness cannot be used as a reliable surrogate for visual outcome in patients with DME.

The anti-inflammatory and anti-angiogenic properties of corticosteroids may be synergistic with current anti-VEGF agents in the treatment of DME. Adjunct use of triamcinolone in the treatment of DME has received considerable attention. Lam et al. evaluated the efficacy of sequential IVT injection followed by grid laser for treating DME. This was a prospective, 3-armed, randomized clinical trial involving 111 eyes. Patients were randomized to grid laser, 4 mg of IVT, or 4 mg of IVT combined with sequential grid laser after 1 month. The interim results of this 2-year trial showed that combined therapy resulted in a greater reduction in macular thickening (58 $\mu m$) and appeared to be superior to IVT alone (20 $\mu m$) at 17 weeks (p = 0.007), but statistical significance was not maintained at 6 months. Difference in BCVA among the 3 groups also did not reach statistical significance. The authors concluded that combined treatment may enhance the short-term efficacy of laser by inducing a greater reduction in macular thickness, but recurrence of DME is common and a greater reduction in macular thickness does not necessarily translate into improved vision.

Avitabile et al. performed a similar, prospective 3-arm randomized clinical trial comparing efficacies of IVT, grid laser alone, and sequential IVT followed by grid laser 3 months later. Patients were observed for a mean of 9 months, and it was demonstrated that eyes treated with 4-mg IVT with or without additional grid laser had significantly larger reduction in macular edema and better mean final VA than eyes treated with laser alone. No significant differences in macular thickness and VA were found between the IVT-alone group and eyes treated with combined IVT and laser at all time points. This led the authors to conclude that additional laser photocoagulation after IVT might not provide an additional benefit.

Kang et al. compared the outcomes of IVT combined with grid laser after 3 weeks to IVT without laser in patients with diffuse DME. Patients who received grid laser after intravitreal TA injection were found to have significantly better BCVA and a greater reduction in macular thickness at 3 and 6 months after treatment. The authors concluded that combined grid laser and IVT maintains improved visual acuity and reduces the recurrence of DME.

These apparently conflicting results support further, rigorous evaluation in larger controlled prospective randomized trials to assess the efficacy of combined treatment modalities for DME, especially over longer treatment periods. Currently such trials are on-going and initial results are expected by early 2010.

The treatment of PDR with PRP remains the current standard of care, being the only modality proven to effectively reduce the long-term incidence of visual loss in these patients. When PDR occurs concurrently with CSME, management becomes more complex. PRP has been reported to cause or worsen CSME, but the
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extent to which this happens under current treatment regimens is unknown and is being evaluated in ongoing studies. Initial animal studies have shown that BRB breakdown after PRP is responsive to corticosteroid treatment. The stabilization of diabetic retinal neovascularization with corticosteroid treatment alone has not yet been reported. Small prospective trials have shown potentially promising results with the addition of intravitreal triamcinolone to PRP in the management of PDR and CSME.62–66

Zein et al. performed a prospective clinical trial of 35 eyes evaluating the adjunct use of IVT with PRP in eyes with PDR and CSME. A retrospective control group was utilized where PRP was combined with focal laser. After 9 months of follow-up, visual acuity was 20/80 in the IVT group versus 20/156 in the laser group (p = 0.007). The authors recommended further evaluation in larger clinical trial to confirm this observed benefit.

Maia et al. reported 1 year outcomes in a randomized clinical trial comparing PRP and focal laser, with PRP and focal laser plus IVT in eyes with PDR and CSME. The BCVA improved, and macular thickness was reduced in the IVT group compared with the laser-only group at all study follow-up visits (p < 0.001). The mean BCVA was 20/25–1 for the IVTA group and 20/40–1 for the control group at 12 months (p < 0.001). The mean macular thickness was 236 µm for the IVTA group and 266 µm for the laser-only group at 12 months (p < 0.001). The authors concluded that the combination of laser photoagulation with IVT was associated with improved BCVA and a greater reduction in macular thickness when compared with laser photoagulation alone for the treatment of PDR with CSME. A large NEI sponsored randomized clinical trial is currently enrolling patients to further evaluate these effects and results are expected in 2010.60

The clinically optimal treatment for DME has not yet been realized. Focal/grid laser still remains the primary treatment option in the management of center involved DME.11,12 However, focal/grid laser probably fails to directly address the underlying pathophysiological mechanisms of DME. In the ETDRS, despite laser treatment 15% of patients still developed MVL after 3 years. Data from a DRCR.net trial has shown that in laser treated eyes, moderate visual loss occurred in 14% and moderate visual gain (improvement of 15 letters or more) was observed in 18%.12

Future efforts to optimally address the treatment of DME must recognize that the pathogenesis of DME may be multifactorial, involving such diverse processes as inflammation, angio/vasculogenesis, junctional mechanisms and actions of a variety of different and possibly independent growth/permeability factors. Combination therapies, targeting multiple distinct pathophysiologic pathways may eventually prove necessary for maximal efficacy. In addition, since the relative contributions of these specific mechanisms may vary between individuals or possibly over time in the same individual, ultimately treatment regimens may need to be tailored to the unique disease profile of the individual patient.

Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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