

The Role of Steroids in the Treatment of Diabetic Macular Edema

Multiple pharmacologic strategies are currently available.

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Diabetic macular edema (DME) is a leading cause of visual impairment that occurs as an increased accumulation of fluid within the intraretinal layers of the macula as a result of microvascular changes and breakdown of the blood-retinal barrier. The standard of care for DME is laser photocoagulation. A substantial group of patients, however, are unresponsive to laser therapy and fail to improve after photocoagulation. Lee and Olk¹ have reported that, 3 years after initial grid treatment, visual acuity improved in 14.5% of eyes, did not change in 60.9%, and decreased in 24.6% of patients with DME. Moreover, new insights in the pathogenesis of macular edema and newer imaging instruments, such as optical coherence tomography, have led to the identification of different forms of this condition that may also respond differently to a number of therapeutic approaches. Consequently, different treatment strategies are being investigated.

In recent years, the intravitreal administration of steroids has provided promising results. A complete understanding of the mechanism of action of corticosteroids has not been fully clarified. The antiinflammatory, angiostatic and antipermeability properties of corticosteroids, however, seem to be related to interference with many regulatory components of gene expression. This includes the inhibition of the expression of vascular endothelial growth factor (VEGF) and key proinflammatory genes (tumor necrosis factor alpha [TNF- α] and other inflammatory chemokines), and the inducing of gene functioning as antiinflammatory factors (pigment-derived growth factor-PEDF).²⁻⁶ The antiinflammatory activity of steroids is also related to the inhibition of the

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phospholipase A2 pathway, to the lower release of inflammatory cell mediators, and to reduced leukocyte chemotaxis.⁷ Additionally, triamcinolone acetonide (TA) seems to reduce the expression of matrix metalloproteinases and to down-regulate intercellular adhesion molecule 1 (ICAM1) on choroidal endothelial cells.⁸

INTRAVITREAL TRIAMCINOLONE ACETONIDE

Intravitreal TA has been used for treatment of DME, and a number of randomized clinical trials have demonstrated significant improvements either in morphological or functional outcomes.⁹⁻¹² A carefully designed prospective randomized trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) investigated the efficacy and safety of 1-mg and 4-mg doses of preservative-free intravitreal TA in comparison with focal or grid laser photocoagulation.¹³ Eight hundred-forty study eyes with DME were randomized to either focal or grid laser photocoagulation (n=330), 1 mg TA (n=256), or 4 mg TA (n=254). At the 2-year primary outcome, the mean $\pm$ SD change in the visual acuity from baseline was 1 $\pm$ 17 letters in the laser group, -2 $\pm$ 18 letters in the 1-mg TA group, and -3 $\pm$ 22 letters in the 4-mg TA group. Mean $\pm$ SD reductions in central macular thickness were 139 $\pm$ 148 μ m in the laser

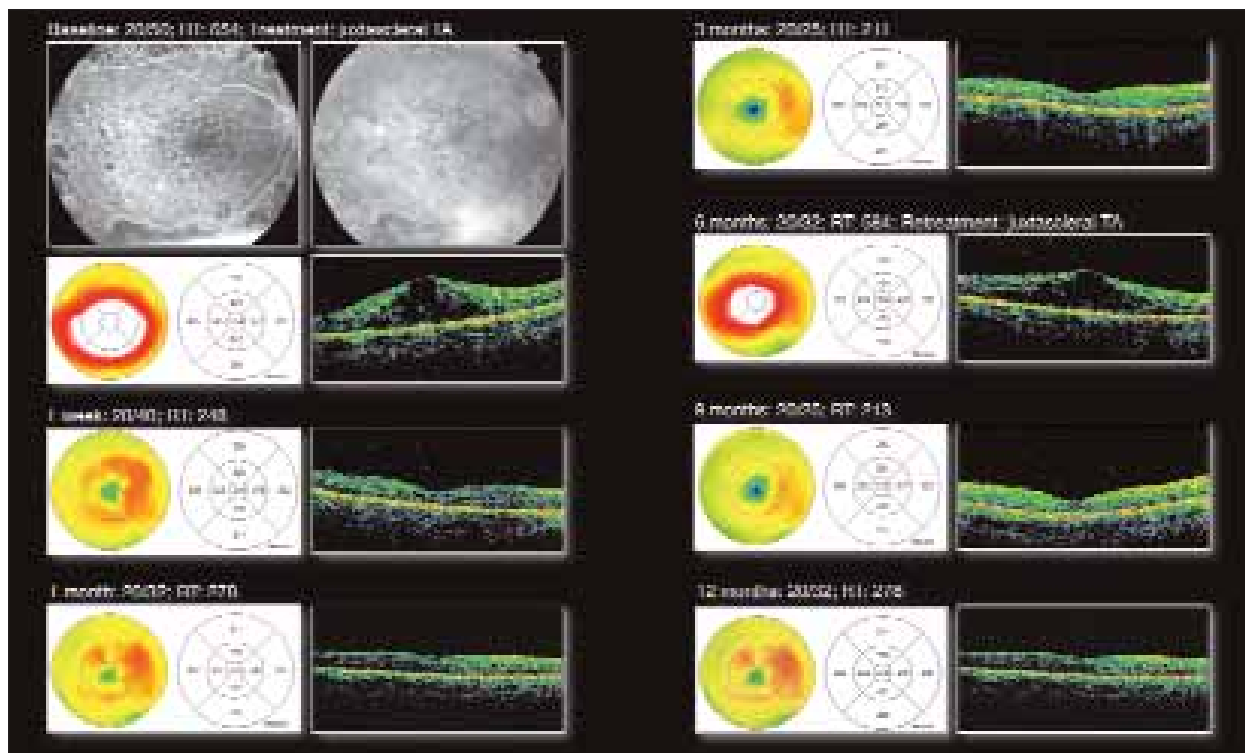


Figure 1. Diffuse diabetic macular edema unresponsive to laser photocoagulation treated with juxtascleral infusion of a modified formulation of triamcinolone acetate. Evolution of tomographic features shows a reduction of macular edema at 1 week and 1 and 3 months. At 6 months, edema recurred and the patient was retreated. The second injection was effective in reducing central retinal thickness at 9 and 12 months. At baseline, fluorescein angiography shows late hyperfluorescence due to a generalized breakdown of the inner blood-retinal barrier.

group, $86 \pm 167 \mu\text{m}$ in the 1-mg TA group, and $77 \pm 160 \mu\text{m}$ in the 4-mg TA group. The mean number of treatments at the end of follow-up was 2.9 for the laser group, 3.5 for the 1-mg, and 3.2 for the 4-mg TA groups. Three-year follow-up data were available in 306 eyes. The mean change in the visual acuity letter score from baseline to 3 years was +5 in the laser group and 0 in both the triamcinolone groups.¹⁴

Although the recent enthusiasm for intravitreal TA has been reshaped by the results of this study, physicians are fully aware that a significant proportion of patients with diffuse DME have poor prognosis despite grid laser photocoagulation.¹ Therefore, intravitreal TA has been tested for these cases of diffuse DME refractory to laser treatment.

Gillies et al¹² reported 2-year outcomes of a randomized trial evaluating the efficacy of repeated intravitreal injections of TA in DME persistent despite laser treatment. Mean improvement in visual acuity was 3.1 letters in the triamcinolone injection group compared with an average loss of 2.9 letters in the control group. Mean retinal thickness reduction was 125 μm in the TA group and 71 μm in the control group. Hauser et al¹⁵ com-

pared the efficacy of different doses of intravitreal TA in eyes with refractory diffuse DME. Forty-five eyes were randomized to receive 1, 2, or 4 mg intravitreal TA. At 24 weeks, visual acuity improvement was 3.4, 8.1, and 4.6 letters in the 1, 2, and 4 mg intravitreal TA groups, respectively. Kim et al¹⁶ studied the efficacy of 2-mg and 4-mg intravitreal TA in refractory DME. Six-month results were available for 25 eyes. At 6 months, visual acuity improvement was 3.7 letters for the 2-mg group and 7.4 for the 4 mg group. Audren et al⁹ reported the results of a 6-month controlled trial. Seventeen patients were enrolled; one eye of each patient was injected with 4 mg TA, while the other eye served as a control. At the end of the study a mean increase in visual acuity of 6.9 letters was observed in the injected eyes, while a mean loss of 3.6 letters was reported in the control eyes. Jonas et al¹¹ examined the visual outcome of patients receiving an intravitreal injection of 20 mg of TA. Visual acuity improved significantly among the 28 eyes included in the study group by 3.4 Snellen lines. Sutter et al¹⁷ evaluated the efficacy of 4 mg intravitreal TA in a 3-month randomized, controlled trial. At the end of the follow-

up, visual acuity change was +5 letters in the treatment group (n=33) and -0.1 letters in the control group (n=32). Beer et al¹⁸ observed that adequate concentrations of TA could provide therapeutic effects for approximately 3 months after 4-mg intravitreal TA injection. Audren et al¹⁹ suggested a maximum effect duration of 140 days. This is consistent with drug efficacy duration after intravitreal injection in previously published clinical trials.

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In regard to adverse events, intravitreal TA injections may carry considerable risk, including acute infectious endophthalmitis, pseudoendophthalmitis and iatrogenic retinal breaks. A recent review reported an estimated incidence of endophthalmitis after intravitreal administration of TA of 1.4% per injection (24/1,739).²⁰ In the DRCR.net study no cases of endophthalmitis or inflammatory pseudoendophthalmitis were reported after any of the 1649 intravitreal injections.¹³

PERIBULBAR TRIAMCINOLONE ACETONIDE

Growing evidence is showing the usefulness of the transcleral pathway in delivering drug to the macular retina.²¹⁻²⁴ Transcleral delivery of TA is routinely used for the treatment of various inflammatory eye diseases, and recently it has been proposed for the treatment of DME. Some studies suggest that intravitreal injection of TA may be more effective than juxtasclear infusion for the treatment of refractory DME. Bonini-Filho et al²⁵ compared the efficacy of posterior sub-Tenon's infusion and intravitreal injection of TA in a randomized trial in 28 eyes with refractory diffuse DME. Retinal thickness significantly improved in the intravitreal TA group when compared with the sub-Tenon's TA group at 2 weeks and 1, 2, 3, and 6 months after treatment ($P<.01$). The authors suggested that this difference may be due in part to reflux of the drug, which was noted in 21.4% of juxtasclear injections. Cardillo et al,²⁶ in a retrospective study on 85 eyes treated with posterior sub-Tenon TA and 41 eyes with intravitreal TA, concluded that in patients with diffuse DME intravitreal injection of TA was more favorable than posterior sub-Tenon's injection for the anatomic and functional aspects of improvement. Other authors have shown more benefit when sub-Tenon TA. Ozdek et al²⁷ retrospectively evaluated the efficacy of posterior

sub-Tenon and intravitreal TA injections in DME refractory to conventional grid laser photocoagulation. The effect of 20 mg/0.5 mL sub-Tenon injection was less dramatic than that of intravitreal TA, although effective both functionally and anatomically with a duration effect of about 3 months. Similarly, Bakri and Kaiser²⁸ showed that 40 mg sub-Tenon injection was beneficial in improving or stabilizing visual acuity in patients with refractory DME. Choi et al²⁹ compared a single 40 mg posterior sub-Tenon injection to intravitreal injection in 60 patients with DME over a 3-month period and concluded that sub-Tenon administration had comparable effect to the intravitreal route with lower risk of elevated intraocular pressure. Cellini et al³⁰ demonstrated that 3 months after administration, intravitreal and sub-Tenon injection of TA produce the same improvement in visual acuity and an equally significant reduction in retinal thickness. Recently, Veritti et al³¹ reported the results of a 12-month study evaluating prospectively the efficacy and safety of posterior juxtasclear infusion of a modified formulation of TA for the treatment of diffuse DME refractory to laser photocoagulation. Modified formulation of TA consisted in a suspension of 40 mg TA, 20 mg sodium chondroitin sulfate, and 15 mg sodium hyaluronate (1.5 mL). Mean improvement in visual acuity among the 22 study eyes was 0.15 logMAR at the end of follow-up. Mean reduction in central retinal thickness was 128 μ m. On average, studied eyes received 1.5 treatments. The authors suggested that the formulation of TA proposed in the study has a duration effect of 6 months (Figure 1). The modified formulation of TA was used in order to enhance its density and viscosity, avoiding reflux and promoting the drugs persistence in the retromacular space. Additionally, the authors postulated that possible interactions between the glycosaminoglycans included in this formulation and those of the scleral matrix may influence the drugs diffusion through the sclera into the eye. Moreover, it is known that sodium hyaluronate may have antiangiogenic properties.³²

CORTICOSTEROID IMPLANTS

Several intravitreal steroid-releasing implants have been designed in an attempt to provide long-term drug delivery to the macular region. These include non-biodegradable and biodegradable dexamethasone, fluocinolone acetonide, and triamcinolone acetonide-implants. Posurdex (Allergan Inc.) is a biodegradable extended-release form of dexamethasone. The polymer matrix composed of poly-lactide-co-glycolide copolymer releases dexamethasone over approximately 1 month, with a therapeutic effect for about 4 months.³³ It is injected via pars plana with a 22-gauge device. Retisert

(Bausch & Lomb) is a nonbiodegradable polymer intravitreal implant designed to release 0.59 mg of fluocinolone acetonide to the posterior segment at an initial rate of 0.6 µg/day, decreasing over the first month to a steady state of 0.3-0.4 µg/day. Drug release can last for a period of 30 months.³⁴ Iluvien (Alimera Sciences) is a nonerodable injectable fluocinolone intravitreal implant studied to deliver a low dose of drug for up to either 18 or 36 months. It delivers either 0.2 µg or 0.5 µg of drug per day. I-vation (SurModics) is a non-biodegradable, helical, metal alloy implant coated with polybutyl methacrylate, polyethylene vinyl acetate polymers and TA.

CONCLUSION

The multiple pharmacologic strategies currently available for the treatment of DME, expand the treatment armamentarium beyond laser photocoagulation. Favorable results has been reported with intravitreal administration of TA in the treatment of DME persistent despite laser photocoagulation. However, intravitreal TA shows a limited duration of action with the need of multiple injections and carries the implicit risks of repeated procedures. Therefore, other treatment modalities are being evaluated. Corticosteroids implants can provide extend release of steroids with long-lasting appropriate therapeutic levels of drug reaching the macular tissue. Peribulbar administration of a modified formulation of triamcinolone acetonide has been described to effectively reduce macular thickening due to diffuse DME unresponsive to conventional grid laser photocoagulation. The modified formulation used in our study accounts for the prolonged action of the drug with a low incidence of side effects thanks to the extraocular delivery route. ■

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