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Review Article

Intravitreal Steroids for the Treatment of Retinal Diseases

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Diabetic macular edema (DME), pseudophakic cystoid macular edema (CME), age-related macular degeneration (AMD), retinal vascular occlusion (RVO), and uveitis are ocular conditions related to severe visual impairment worldwide. Corticosteroids have been widely used in the treatment of these retinal diseases, due to their well-known antiangiogenic, antiedematous, and anti-inflammatory properties. Intravitreal steroids have emerged as novel and essential tools in the ophthalmologist's armamentarium, allowing for maximization of drug efficacy and limited risk of systemic side effects. Recent advances in ocular drug delivery methods led to the development of intraocular implants, which help to provide prolonged treatment with controlled drug release. Moreover, they may add some potential advantages over traditional intraocular injections by delivering certain rates of drug directly to the site of action, amplifying the drug's half-life, contributing in the minimization of peak plasma levels of the drug, and avoiding the side effects associated with repeated intravitreal injections. The purpose of this review is to provide an update on the use of intravitreal steroids as a treatment option for a variety of retinal diseases and to review the current literature considering their properties, safety, and adverse events.

1. Introduction

The use of corticosteroids for the treatment of ocular inflammatory diseases was first described in the early 1950s [1]. Corticosteroids have anti-inflammatory, antiangiogenic, and antipermeability properties that make them an attractive therapeutic option for a variety of posterior segment diseases. The rationale for using a steroidal drug for the treatment of edematous and proliferative diseases is that abnormal proliferation of cells is often associated with and trigged by inflammation. Moreover, intraretinal accumulation of fluid is usually accompanied by a blood-retinal barrier dysfunction that can be restored with steroid therapy. The principal effects of steroids are thought to be stabilization of the blood-retinal barrier (BRB), reduction of exudation, and downregulation of inflammatory stimuli, but the exact mechanisms remain unknown. Steroids are thought to act by the induction of proteins called lipocortins, in particular phospholipase A2. These proteins reduce leukocyte chemotaxis, control biosynthesis, and inhibit the release of arachidonic acid from the phospholipid membrane, which is one of the most important common precursors of potent inflammatory cell mediators such as prostaglandins and leukotrienes. Based on experimental studies, corticosteroids have been shown to control gene expression of inflammatory mediators. This regulation influences the expression of vascular endothelial growth factor (VEGF), inhibits pro-inflammatory genes such as tumor necrosis factor-alpha (TNF-α) and other inflammatory chemokines, and induces the expression of anti-inflammatory factors such as pigment-derived growth factor (PEDF) [2–4]. Additionally, steroids seem to reduce the expression of matrix metalloproteinases (MMPs) and to downregulate intercellular adhesion molecule 1 (ICAM-1) on choroidal endothelial cells [5–11]. Several routes of administration have been considered for the treatment of various ocular diseases. Oral dosing, unfortunately, causes a spectrum of systemic side effects, including osteoporosis, cushingoid state, adrenal suppression, and exacerbation of diabetes [12, 13]. Topical steroids have not been shown to penetrate adequately to the posterior segment [14]. Geroski and Edelhauser reported that therapeutic doses of steroids could reach the posterior segment via transscleral absorption with periocular administration [15]. Thus, other routes of administration, such as subconjunctival, subtenon,

and posterior juxtascleral infusions, have been studied [16–18]. Periocular delivery of steroids has offered for many years a valid compromise between better penetration and lack of systemic side effects. However, peribulbar injections seem to result in lower morphological and functional outcomes as compared with those reported with the use of intravitreal administration [19–22]. But, two interventional case series have demonstrated that posterior juxtascleral infusion of a viscoelastic formulation of triamcinolone acetonide is an effective treatment for diffuse diabetic macular edema (DME) unresponsive to laser photocoagulation [23, 24].

Based on experimental studies, clinical observations, and pathogenic considerations, Robert Machemer, among others, suggested the intravitreal delivery of steroids to locally suppress intraocular inflammation, proliferation of cells, and neovascularization [25]. Intravitreal delivery of corticosteroids has allowed many posterior segment diseases to be locally treated without the adverse systemic side effects. Intravitreal steroids have been widely studied in many randomized clinical trials, demonstrating significant improvements both in morphological and functional outcomes in many posterior segment diseases [26–28]. Intravitreal therapy also allows for the steroid to bypass the BRB, leading to a more concentrated dose of steroid for a prolonged period of time. Delivery of steroids to the vitreous cavity can be achieved via direct injection through the pars plana, introduction of a sustained-release or biodegradable implants, or injection of conjugate compounds. Several intravitreal biodegradable and nondegradable steroid releasing implants have been designed to provide long-term drug delivery to the macular region. Different steroid molecules have varying potencies and toxicities. There are several ways to distinguish among the steroids used in ophthalmology, including chemical structure, anti-inflammatory potency, ability to translocate the glucocorticoid receptor complex to the nucleus, ability to transactivate or transrepress ligand-dependent gene sets and biologic responses, neuroprotection of the photoreceptors/retinal pigment epithelium, and direct cytotoxic effects [29]. These differences may help to explain the differences among steroids in their safety and efficacy for the treatment of retinal disease. The purpose of this paper is to review the current status of intravitreal steroidal drugs, including triamcinolone acetonide, biodegradable dexamethasone implant, and nondegradable fluocinolone acetonide implant in the treatment of various retinal diseases such as diabetic macular edema (DME), central and branch retinal vein occlusion (CRVO and BRVO), neovascular age-related macular degeneration (AMD), pseudophakic cystoid macular edema (CME), and macular edema secondary to uveitis.

2. Triamcinolone Acetonide

Triamcinolone acetonide (TA) is a synthetic steroid of the glucocorticoid family with a fluorine in the ninth position [30]. It is commercially available as an ester and represents one of the most commonly used steroid agents for the

anti-inflammatory potency five times higher than hydrocortisone with a tenth of the sodium-retaining potency. It appears as a white- to cream-colored crystalline powder and it is practically insoluble in water and very soluble in alcohol [14]. The decreased water solubility accounts for its prolonged duration of action. It has been observed that adequate concentrations of TA could provide therapeutic effects for approximately three months after 4 mg intravitreal TA injection [32]. Maximum effect duration of 140 days has been suggested [33].

The current commercial preparations of TA include products that received dermatologic and orthopedic indications and are considered off-label for the intraocular use, products registered as devices for assisting the visualization of the vitreous during vitreoretinal procedures, and products that are registered for intraocular use in uveitis, and other ocular inflammatory conditions. Kenalog-40 (40 mg/mL, Bristol-Myers Squibb, NJ) is the most commonly used intraocular steroid and has been widely utilized as intravitreal injections since 2004 for the treatment of several retinal diseases. This formulation is US Food and Drug Administration (FDA)-approved only for intramuscular and intra-articular use and is currently employed off-label for intraocular injections. TrivarisTM (80 mg/mL, Allergan Inc., Irvine, CA) and Triesence (40 mg/mL, Alcon Inc., Fort Worth, TX) are preservative-free brands of TA recently FDA approved for ophthalmic use in the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and other ocular inflammatory diseases, unresponsive to topical corticosteroids. Vitreal S (Sooft s.p.a., Fermo, Italy) is a medical device used in endocular surgery to stain the vitreous during vitrectomy and it is not registered as drug for intraocular use. There are some issues regarding the formulation of TA used for intraocular administration. A previous phase-contrast microscopy study showed a notable difference of crystal size depending upon the drug formulation [34]. Very large and irregular crystals, with a significant heterogeneity in crystal size, were occasionally found in the off-label, commercially available, benzyl-alcohol-preserved TA, whereas the crystals of a preservative-free in-label, commercially available, TA suspension appeared to be relatively uniform in size. These morphologic aspects may have a significant impact on the half-life of the drug both in vivo and in vitro. This hypothesis is based on the fact that smaller crystals have a superior surface-area-to-volume ratio, allowing them to be dissolved more rapidly. The formulations containing crystals that widely vary in size and, thus, including larger crystals may theoretically generate a wider time–drug concentration curve because of their slower dissolution rate. Different TA formulations show variance in reducing the endothelial cell proliferation.

The appropriate dose of intravitreal TA remains a subject of debate. Both Audren et al. and Hauser et al. showed that the use of a 4 mg dose of intravitreal TA does not have enough advantages over the lower 1 mg or 2 mg dose [35, 36]. However, Lam et al. published a comparison between 4 mg and 8 mg doses and showed that the higher dose had a more sustained effect on both visual acuity and central

complications [37]. By using a dose of about 20 mg of TA, the increase in visual acuity was mostly marked during the first three and six months after injection and was observable for a period of about six to nine months. Differently, by using a dose of 4 mg, the duration in the reduction of macular thickness as measured by optical coherence tomography (OCT) was less than six months [38].

Based on several studies, intravitreal administration of triamcinolone acetonide (TA) has provided promising results for the treatment of disorders associated with an abnormal endothelial cell proliferation and conditions complicated by intraretinal and subretinal fluid accumulation. The anti-inflammatory, angiostatic, and antipermeability properties of TA have gained interest in chronic retinal diseases, such as proliferative diabetic retinopathy [39], DME [40, 41], exudative AMD [42–44], presumed ocular histoplasmosis syndrome [45], CRVO [46], BRVO [47], neovascular glaucoma [48], proliferative vitreoretinopathy [49], persistent pseudophakic CME [50], perifoveal telangiectasias [51], sympathetic ophthalmia [52], ischemic ophthalmopathy [53], exudative retinal detachment [54], radiation induced macular edema [55], macular edema due to retinitis pigmentosa [56], Vogt-Koyanagi-Harada syndrome [57], and chronic uveitis [58].

2.1. Diabetic Macular Edema. Intravitreal TA has been widely studied in many randomized clinical trials on DME demonstrating significant improvements both in morphological and functional outcomes [40, 41, 59–61]. Focal and grid laser photocoagulation have been considered the standard of care for the treatment of DME for many years. However, a substantial group of patients are unresponsive to laser therapy and fail to improve after photocoagulation. It has been reported that three years after initial grid treatment, visual acuity improved in 14.5% of the eyes, did not change in 60.9%, and decreased in 24.6% of patients with DME [59]. Therefore, TA has been tested for the treatment of DME, either naïve or diffuse and refractory to laser therapy. In most cases, TA has been administered intravitreally.

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 (Trivaris) in comparison with focal or grid laser photocoagulation [60]. In the DRCR.net study, 840 study eyes affected by DME were randomized to either focal or grid laser photocoagulation ($n = 330$), 1 mg TA ($n = 256$) or 4 mg TA ($n = 254$). At 36 months, the mean change in the visual acuity from baseline was +5 letters in the laser group and 0 letters in both TA groups. A worsening in visual acuity of three or more lines occurred in 8%, 17%, and 16% of eyes, respectively, and an improvement in visual acuity by three or more lines occurred in 26%, 20%, and 21% of eyes, respectively. Mean (±SD) reductions in central macular thickness were 175 ± 149 μm in the laser group, 124 ± 184 μm in the 1 mg TA group, and 126 ± 159 μm in the 4 mg TA group. The mean number of treatments at the end of the follow-up was 3.1 for the laser group, 4.2 for the 1 mg, and 4.1 for the 4 mg TA groups. At the four-month visit, mean visual acuity improvement was higher in the 4 mg TA group (4 ± 12 letters improvement) than in either the laser group (0 ± 13 letters change) or the 1 mg TA group (0 ± 13 letters change). By 12 months, there were no significant differences among groups in mean visual acuity. Therefore, in this study, photocoagulation was shown to be more effective over time and had fewer side effects than TA. This was considered in support of focal/grid photocoagulation. However, it must be noted that during the 36 months of follow-up, patients received only four treatments with intravitreal TA, which is a low reinjection rate based on pharmacokinetic data. Recently, a new, large, randomized DRCR.net study investigated the efficacy of intravitreal TA in combination with laser photocoagulation in comparison with intravitreal ranibizumab with prompt or deferred laser photocoagulation or laser photocoagulation alone. At 2-year visit, mean change (±SD) in the visual acuity letter score from baseline was +7 ± 13 in the ranibizumab + prompt laser group, +9 ± 14 in ranibizumab + deferred laser group, +2 ± 19 in the TA + prompt laser group, and +3 ± 15 the sham + prompt laser group. Compared with the sham + prompt laser group, the difference in mean change in the visual acuity letter score from baseline was 3.7 letters greater in the ranibizumab + prompt laser group ($P = 0.03$), 5.8 letters greater in the ranibizumab + deferred laser group ($P < 0.01$), and 1.5 letters worse in the TA + prompt laser group ($P = 0.35$). A worsening of visual acuity of three or more lines occurred in 10%, 4%, 2%, and 13% of eyes, respectively, and an improvement in visual acuity by three or more lines occurred in 18%, 29%, 28%, and 22% of eyes, respectively. The mean change (μm ± SD) in central retinal thickness from baseline was −141 ± 155 in the ranibizumab + prompt laser group, −150 ± 143 in ranibizumab + deferred laser group, −107 ± 145 in the TA + prompt laser group, and −138 ± 149 the sham + prompt laser group. Compared with the sham + prompt laser group, the difference in mean change in central macular thickness from baseline was 31 μm worse in the ranibizumab + prompt laser group ($P = 0.03$), 28 μm worse in the ranibizumab + deferred laser group ($P = 0.01$), and 10 μm worse in the TA + prompt laser group ($P = 0.37$). These results showed that intravitreal ranibizumab with prompt or deferred laser is more effective than prompt laser alone or intravitreal TA combined with laser for the treatment of DME involving the central macula. Among the eyes that were pseudophakic at baseline, the mean change (±SD) in the visual acuity letter score from baseline was +5 ± 17 in the ranibizumab + prompt laser group, +9 ± 17 in ranibizumab + deferred laser group, +8 ± 13 in the TA + prompt laser group, and +5 ± 15 the sham + prompt laser group. The difference in mean change in visual acuity letter score from baseline to the two-year visit was 1.6 letters greater in the TA + prompt laser group compared with the sham + prompt laser group and was similar to difference in outcomes between the ranibizumab + prompt laser group (+0.5 letters) and the ranibizumab + deferred laser group (+3.5 letters) compared with the sham + prompt laser group. Cataract surgery was required in 12% of phakic eyes in the sham + prompt laser and in the ranibizumab + prompt laser groups, in 13% of phakic eyes in the ranibizumab + deferred laser group, and in 55%

of patients of the TA + laser group. An intraocular pressure (IOP)-lowering medication was required in 5% of eyes in the sham + prompt laser and ranibizumab + prompt laser groups, in 3% of eyes in the ranibizumab + deferred laser group, and in 28% of patients of the TA + laser group [61]. Other studies demonstrated promising results of combination therapy with intravitreal injection of TA and laser photocoagulation for the treatment of proliferative diabetic retinopathy (PDR) with clinically significant macular edema (CSME) [62–67]. In a 12-month randomized clinical trial conducted by Maia et al., 44 eyes with PDR and CSME were enrolled and randomized to treatment with combined 4 mg of intravitreal TA and laser photocoagulation ($n = 22$) or to laser photocoagulation alone ($n = 22$). Mean best correct visual acuity (BCVA) improved significantly ($P < 0.001$) in the TA and laser group compared with the laser alone group at all study follow-up visits. An improvement of two or more Early Treatment Diabetic Retinopathy Study (ETDRS) lines was observed in 63.1% and 10.5% of eyes, respectively ($P < 0.001$). A significant decrease in mean central macular thickness occurred in the TA and laser group when compared with the laser alone group at all study follow-up intervals ($P < 0.001$). At 12 months, mean (±SD) reductions in central macular thickness were 123 ± 68 μm and 65 ± 51 μm, respectively ($P < 0.001$) [67]. Several other studies reported positive results of intravitreal TA in refractory DME [68–71]. In a six-month prospective, placebo-controlled, randomized clinical trial conducted by Jonas et al., 40 eyes with persistent DME were enrolled and randomized to treatment with 20 mg TA ($n = 28$) or to placebo injection ($n = 12$). Visual acuity increased significantly ($P < 0.001$) in the TA group by 3.4 ETDRS lines. In the placebo group, visual acuity did not change significantly ($P = 0.07$) during the six months. At the end of the follow-up period, 48% in the TA group improved by at least two ETDRS lines compared with 0% eyes in the placebo group [69]. Recently, Gillies et al. reported the longest-term data available concerning the outcomes of intravitreal injection of TA. This was a five-year prospective, double-masked, randomized clinical trial of 4 mg dose of preservative-free intravitreal TA in comparison with placebo. In this study, 67 study eyes with refractory DME were randomized to receive 4 mg TA ($n = 33$) or placebo ($n = 34$). At five years, an improvement in visual acuity of three or more lines occurred in 42% of the eyes in the TA group and 32% of eyes in the placebo group ($P = 0.4$). A worsening of visual acuity by three or more lines occurred in 18% and 24% of eyes, respectively ($P = 0.88$). Mean (±SD) reductions in central macular thickness were 100 ± 79 μm in the TA group and 184 ± 29 μm in the placebo group ($P = 0.45$). After five years, the difference in visual acuity between the two groups was not statistically significant and there was no difference in mean central macular thickness reduction between two groups. Moreover, this study showed that, in the long term, a two-year delay in the beginning of intravitreal TA treatment did not seem to adversely affect outcomes in eyes affected with refractory DME [70].

Novel preservative-free and sustained-release intravitreal implants have been evaluated for the treatment of DME to

administration frequency and minimal side effects. I-vation (SurModics, Eden Prairie, MN, USA) is a nonbiodegradable, helical, metal alloy implant coated with polybutyl methacrylate, polyethylene vinyl acetate polymers, and TA. Drug delivery and duration rates can be tuned varying the ratios of the constituent polymers. This system is implanted through a 25-gauge device. A phase I study have shown positive functional and morphological outcomes in 31 patients affected by DME [71]. However, phase IIb trial for I-vation TA was suspended in 2008 following the publication of the DRCR.net study. The Cortiject implant (NOVA63035, Novagali Pharma) is a preservative- and solvent-free emulsion that contains a tissue-activated proprietary corticosteroid prodrug. Once released, the prodrug is activated at the level of the retina. A single intravitreal injection of the emulsion provides sustained release of the corticosteroid over a 6- to 9-month period. An open-label, phase 1, dose-escalation clinical study to assess the safety and tolerability of NOVA63035 in patients with DME is currently underway.

2.2. Macular Edema Secondary to Retinal Vein Occlusion. Macular edema is a common cause of reduced vision in patients with retinal vein occlusions. Due to the well-know antiedematous and antipermeability effects, intravitreal TA has been evaluated in many studies on macular edema secondary to CRVO and BRVO. Case series have suggested that intravitreal injection of TA may be useful for the treatment of macular edema in patients with BRVO [72]. However, the use of this pharmacological approach was not supported by the results presented in the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study. In this multicenter clinical trial, 411 participants affected by macular edema secondary to BRVO were randomized to receive laser photocoagulation, 1-mg, or 4-mg doses of preservative-free intravitreal TA (Trivaris). After 12 months of follow-up, the proportion of eyes with an improvement in visual acuity that enabled patients to read 15 or more letters was similar among the three groups (27% in the group treated with the 4-mg dose of TA, 26% in the group treated with the 1-mg dose, and 29% in the control group). Results showed that there was no difference identified in visual acuity at 12 months for the laser group compared with the TA groups. The duration of the edema is an important issue to be considered. Among patients with a duration of macular edema that is more than 3 months, a proportion of 34% of eyes showed a gain of 15 letters or more in the 4-mg TA group, versus a percentage of 15% of patients in the photocoagulation group. However, these findings were not statistically significant but indicated the importance of taking into account the duration of edema in data analysis and in clinical practice [47]. Several clinical trials have also published the beneficial effects of intravitreal administration of TA for the treatment of macular edema due to CRVO [73]. In a 12-month randomized clinical trial, 271 patients affected by macular edema secondary to nonischemic CRVO were randomly assigned to observation, 1-mg or 4-mg doses of preservative-free intravitreal TA (Trivaris). At 1 year, the

15 or more letters was 26% in the group treated with the 4-mg dose of TA, 27% in the group treated with the 1-mg dose, and 7% in the control group ($P = 0.001$) [46]. Verisome (Icon Bioscience Inc, Sunnyvale, CA, USA) is a biodegradable implant designed to be injected intravitreously and release TA for up to one year.

The Verisome delivery system is a sustained-release drug delivery system that can be injected into the eye as a liquid via a standard 30-gauge needle. When injected into the vitreous, the liquid coalesces into a single spherule. A phase I trial was conducted in patients with macular edema associated with RVO evaluating the drug delivery system at two dosing levels, a 25-μL dose designed to last 6 months, and a 50-μL dose designed to last one year in the vitreous cavity. The promising results of the clinical trial confirmed the safety and efficacy outcomes and the controlled-release attributes of the technology [74].

2.3. Pseudophakic Cystoid Macular Edema. Postoperative cystoid macular edema may be a complication of cataract surgery. This condition is typically treated with topical, peribulbar, and systemic administration of steroids and nonsteroidal anti-inflammatory agents. Recently, promising results have been obtained using intravitreal TA for the treatment of this condition [50].

2.4. Other Indications. Intravitreal administration of TA has been increasingly performed as an alternative option for the treatment of exudative age-related macular degeneration either in monotherapy or in combination with anti-VEGF drugs. Furthermore, TA has recently been used in combination with pars plana vitrectomy for proliferative diabetic retinopathy and proliferative vitreoretinopathy. Intravitreal TA is also a useful surgical tool for assisting vitreoretinal surgery because besides visualizing the vitreous body, it allows a sharp contrast between the peeled and unpeeled retina, promoting the removal of the membranes that are readily visualized. TA-assisted peeling has been reported during macular hole and macular pucker surgery [75]. Other conditions that can benefit from intravitreal TA are uveitis and immunological disorders, cystoid macular edema after penetrating keratoplasty, and progressive ocular hypotony [76, 77].

3. Dexamethasone

Dexamethasone is a potent inhibitor of cytokines released by human pericytes and it has demonstrated high levels in the vitreous for more than 6 months in vivo. Preclinical studies have reported that intravitreal injection of dexamethasone decreases significantly Intercellular Adhesion Molecule-1 (ICAM-1) mRNA, and protein levels, reducing leukostasis and BRB breakdown [78]. Dexamethasone has a relatively short half-life (about 3.5 hours), but is five times more potent than TA [79, 80]. An innovative intravitreal dexamethasone implant has been developed to permit a sustained and extended release of corticosteroids in the intravitreal cavity. A biodegradable dexamethasone drug delivery system (DDS) has been created by Allergan (Ozurdex, Allergan, Irvine, CA, USA). Ozurdex was designed to provide sustained distribution of 700 μg of dexamethasone in the vitreous cavity. The implant is formed by a solid biodegradable polymer (NovadurTM, Allergan, Irvine, CA, USA), whose degradation produces lactic acid and glycolic acid, which are subsequently converted to and eliminated as carbon dioxide and water. The dexamethasone implant is administered as an office-based intravitreal injection using a novel 22-gauge injecting applicator [81]. Recently, Chang-Lin et al. have published pharmacokinetics and pharmacodynamics data of Ozurdex. It was observed that the opaque, round cylindrical implant became translucent, fragmented, and smaller two months after implantation. The concentration of dexamethasone was detected in the retina and vitreous humor for 6 months, with peak concentrations during the first 2 months. Dexamethasone concentrations in the vitreous and in the retina were characterized by two distinct phases, which corresponded to the fragmentation of the implant. On day 60, high levels of dexamethasone were detected in the posterior segment, with the mean peak concentration of 1110 ± 284 ng/g in the retina and 213 ± 49 ng/mL in the vitreous. Following a relatively rapid decline in concentration between day 60 and 90, a second steady state is reached and maintained through day 180 [82].

The Ozurdex dexamethasone-sustained delivery implant has been approved by the United States Food and Drug Administration (FDA) for the treatment of macular edema associated with retinal vein occlusion (RVO) and for noninfectious posterior uveitis.

3.1. Macular Edema Secondary to Retinal Vein Occlusion. FDA approval was based on the therapeutic effects of dexamethasone implant investigated in a randomized, controlled clinical trial (the Ozurdex GENEVA study) [83]. The study design included two identical, randomized, prospective, multicenter, masked, and sham-controlled parallel groups. In the double-masked 6-month initial treatment phase, 1.262 eyes were randomized to either a sham procedure ($n = 426$) or treatment with 350 μg ($n = 414$) or 700 μg ($n = 427$) dexamethasone implant. In the second open-label phase, all eligible eyes received a 700 μg dexamethasone implant and were followed-up for additional 6 months. The primary endpoint was the time to achieve over 15-letter improvement (3 Snellen lines) in BCVA, and the secondary outcomes included BCVA over the 6-month trial period and central retinal thickness measured by OCT. The proportion of eyes that achieved an improvement in visual acuity of 15 or more letters was 22% in the 700 μg group, 23% in the 350 μg group, and 13% in the sham group at month 3 ($P < 0.001$). These data were no longer statistically significant at month 6. At the end of the follow-up, the percentage of eyes that had experienced a three-line gain was 41% in the 700 μg group, 40% in the 350 μg group, and 23% in the sham group ($P < 0.001$). The reduction in mean central retinal thickness was greater in the 700 μg (208 ± 201 μm) and 350 μg (177 ± 197 μm) groups than in the sham group (85 ± 173 μm) at month 3 ($P < 0.001$), but not statistically significant at month 6. Twenty-one percent

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