

Critical appraisal of the clinical utility of the dexamethasone intravitreal implant (Ozurdex[®]) for the treatment of macular edema related to branch retinal vein occlusion or central retinal vein occlusion

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Abstract: Macular edema is a common cause of visual loss in patients with retinal vein occlusions. Ozurdex[®], a dexamethasone intravitreal implant, has been shown in randomized controlled trials to reduce macular edema and improve visual acuity in patients with either branch retinal vein occlusions or central retinal vein occlusions. It was approved in the United States in 2009. Since then, new therapeutic agents and clinical data have emerged. The purpose of this review is to critically evaluate the clinical utility of Ozurdex[®] in the current treatment strategy of macular edema related to retinal vein occlusion.

Keywords: macular edema, branch retinal vein occlusion, central retinal vein occlusion, dexamethasone, Ozurdex[®]

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy.¹ Macular edema is an important cause of visual loss in patients with branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). In 2009, Ozurdex[®], a dexamethasone (DEX) intravitreal implant (Allergan, Inc., Irvine, CA) became the first therapy approved by the US Food and Drug Administration (FDA) for this indication. A year later, ranibizumab (Lucentis[®], Genentech Inc., South San Francisco, CA), a monoclonal antibody fragment that binds to and inhibits vascular endothelial growth factor (VEGF), became the second therapy to be approved. Currently, the off-label use of intravitreal triamcinolone acetonide (TA), and bevacizumab (Avastin[®], Genentech Inc., South San Francisco, CA), another VEGF inhibitor, are also popular treatments for macular edema secondary to RVO.

During the past 2 decades, the management of macular edema associated with RVO has been influenced largely by 2 pivotal trials conducted by the National Institutes of Health (NIH): the Branch Vein Occlusion Study (BVOS) and the Central Vein Occlusion Study (CVOS). In BVOS, patients with BRVO, macular edema with best-corrected visual acuity (BCVA) of 20/40 or worse, and no macular nonperfusion on fluorescein angiography (n = 139) were randomized to focal argon laser photocoagulation or no treatment.² After 3 years of follow-up, the laser group (n = 48) gained an average of 1.33 lines compared with 0.23 lines in the nontreatment group (n = 35; *P* = 0.001). It was observed that macular edema spontaneously resolved in up to one-third of patients.

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Therefore, the investigators from the BVOS recommended waiting 3 months before considering laser treatment. In the CVOS, patients with CRVO and macular edema with BCVA of 20/50 or worse ($n = 155$) were randomized to grid laser photocoagulation ($n = 77$) or no treatment ($n = 78$).³ Although there was a reduction in macular edema on fluorescein angiography (31% of laser group versus 0% of no treatment group) at the 1-year follow-up, there was no difference in BCVA between the 2 groups at any time point over a 3-year period. The CVOS investigators did not recommend laser treatment for CRVO. Until recently, there was no proven, effective therapy for vision loss associated with macular edema secondary to CRVO.

Corticosteroids exhibit anti-inflammatory properties, reduce vascular permeability, inhibit fibrin deposition, stabilize endothelial cell tight junctions, and inhibit the synthesis of VEGF, prostaglandins, and other cytokines.⁴ Small case series were published in 2002 supporting the use of triamcinolone, in the form of Kenalog®-40 (40 mg/L TA suspension, Bristol-Myers Squibb, Princeton, NJ), but the data were limited by small sample size, weak methodology, and lack of appropriate controls. The NIH sought to evaluate TA in the form of Trivaris® (Allergan Inc, Irvine, CA) for BRVO and CRVO in a randomized controlled fashion. The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study compared 1-mg and 4-mg intravitreal triamcinolone with standard of care (grid photocoagulation in eyes without dense hemorrhage and deferral of photocoagulation until hemorrhage clears in eyes with dense macular hemorrhage for BRVO and observation for CRVO).^{5,6} At the 12-month visit, there was no statistically significant difference in VA among the 3 groups with BRVO. However, the adverse rate event, particularly elevated intraocular pressure and cataract, were highest in the 4-mg group. The SCORE investigators advised that grid photocoagulation remain the benchmark against which other treatments are compared in clinical trials evaluating BRVO.

In contrast, intravitreal triamcinolone was determined to be superior to observation for macular edema in patients with CRVO. There was no statistically significant difference in efficacy between the 1-mg and 4-mg groups but the adverse rates of elevated intraocular pressure and cataract were higher in the 4-mg group. The SCORE investigators recommended 1-mg intravitreal triamcinolone for up to 1 year and possibly 2 years.

Design and pharmacology of Ozurdex®

DEX is a water-soluble, synthetic glucocorticoid that is three times more potent than TA⁷ on a molar basis.

Intravitreal injection directly delivers the drug to the vitreous but DEX is rapidly cleared from the vitreous with an estimated half-life of 5.5 hours in humans.⁸ The DEX intravitreal implant contains poly(D,L-lactide-co-glycolide) which degrades into lactic acid and glycolic acid. The drug-copolymer complex is inserted into the eye through the pars plana using a 22 gauge injector and releases a total dose of 0.7 mg of DEX.

Chang-Lin et al recently published their results on the pharmacokinetics and pharmacodynamics of Ozurdex®.⁹ They inserted 0.7 mg DEX implants into both eyes of 34 male monkeys (*Macaca fascicularis*) and collected blood, vitreous humor, and retina samples at days 7, 30, 60, 90, 120, 150, 180, 210, 240, and 270 after administration. Three monkeys without implants served as the control group. DEX was quantified by liquid chromatography-tandem mass spectrometry while gene expression of the DEX-sensitive gene cytochrome P450 A38 (*CYP3A8*) was evaluated by real-time reverse transcription-polymerase chain reaction as a marker of biological activity. It was observed that the opaque, round cylindrical implant became translucent, fragmented, and smaller after day 60. DEX was detected in the retina and vitreous humor for 6 months, with peak concentrations during the first 2 months. After 6 months, DEX was below the limit of quantitation. DEX concentrations in the retina were characterized by 2 distinct phases, which corresponded to the fragmentation of the implant. From days 7 to 60, high concentrations of DEX were detected, with the mean peak DEX concentration ($C_{max} = 1110 \pm 284$ ng/g) recorded on day 60. From days 90 to 210, low concentrations of DEX were detected with the mean concentration at the last detectable time of $C_{last} = 0.0167 \pm 0.0193$ ng/g at day 210. DEX concentrations in the vitreous humor were also characterized by two distinct phases (days 7 to 60 and days 90 to 180). $C_{max} = 213 \pm 49$ ng/mL measured at day 60. $C_{last} = 0.00131 \pm 0.00194$ ng/mL at day 180. In comparison, a standard 0.4-mg intravitreal injection of TA in humans provides an initial concentration of 100,000 ng/mL assuming a 4-mL vitreous humor volume. DEX was present at low concentrations in plasma at all time points. Biodegradable implants typically follow a triphasic drug release pattern consisting of an initial drug burst, sustained release, and a final drug burst.^{10,11} But Ozurdex® does not exhibit a final drug burst. Compared with control eyes, *CYP3A8* expression in the retina was upregulated 3-fold up to 6 months after injection of the implant. The steady state concentrations of DEX observed in monkey eyes are expected to be similar to those in humans.

Efficacy studies, including comparative studies

Two randomized, prospective, masked, sham-controlled studies were conducted at 167 clinical sites in 24 countries to evaluate the safety and efficacy of Ozurdex[®] over an initial 6-month period followed by a 6-month open-label extension (unpublished data).¹² The results were pooled for analysis because the study designs were identical. Patients had to be at least 18 years of age with decreased vision due to clinically detectable macular edema related to CRVO or BRVO. Duration of ME had to be between 6 weeks and 9 months for CRVO and between 6 weeks and 12 months for BRVO. Only 1 eye per patient could be selected. If both eyes were eligible, then the eye with the shorter duration of ME was selected. BCVA was between 34 letters (20/200) and 68 letters (20/50) in the study eye and better than 34 letters in the fellow eye. Retinal thickness in the central subfield on OCT had to be greater than 250 microns in the study eye. Key exclusion criteria included the presence of clinically significant epiretinal membrane, active retinal or optic disc neovascularization, active or history of choroidal neovascularization, presence of rubeosis iridis, any active infection, aphakia or anterior chamber intraocular lens, clinically significant media opacity, glaucoma, or current ocular hypertension requiring more than 1 medication to control intraocular pressure in the study eye, or a history of steroid-induced intraocular pressure rise in either eye. Patients were also excluded if they had diabetic retinopathy in either eye, had any uncontrolled systemic disease, were currently using or anticipating the use of systemic steroids or anticoagulants during the study, or had any ocular condition in the study eye which, in the opinion of the investigator, would prevent a 15-letter improvement in visual acuity. Patients were randomized to either a sham procedure (n = 426) or treatment with 0.35 mg (n = 414) or 0.7 mg (n = 427) DEX implant using a 1:1:1 allocation ratio. The sham procedure followed the same anesthetic and preparation protocol as the treatment arm but used a needleless applicator placed against the conjunctiva to simulate placement of study medication. Patients did not receive grid photocoagulation in the control arm. Randomization was performed using an interactive voice response system and stratified by BRVO or CRVO. All patients were examined at baseline, and at 1, 7, 30, 60, 90, and 180 days after treatment. Masked graders at a central reading center (University of Wisconsin Fundus Photograph Reading center) evaluated OCT measurements using a standard protocol. The intent-to-treat population was used for data

analysis. Initially, the primary outcome for the first study was the proportion of eyes achieving at least a 15-letter improvement from baseline at day 180. The FDA later changed the primary outcome for the second study to be the time to reach a 15-letter improvement from baseline. When interpreting the results, it is important to note that Ozurdex[®] is meant to release intraocular levels of dexamethasone for 6 months. Following completion of the first portion of the study, patients were eligible to have open label retreatment with Ozurdex 0.7 mg regardless of which initial treatment group they were in, sham, 0.35 mg, or 0.7 mg, provided that they demonstrated evidence of comparable macular edema on OCT examination at 6 months.

The cumulative response rate was 41% in the 0.7 mg group, 40% in the 0.35 mg group, and 23% in the sham group ($P < 0.001$). Although the proportion of eyes achieving at least a 15-letter improvement from baseline BCVA was greater in the treatment groups at month 1 (21% in the 0.7 mg group vs 18% in the 0.35 mg group vs 8% in the sham group; $P < 0.001$) and month 3 (22% in the 0.7 mg group vs 23% in the 0.35 mg group vs 13% in the sham group; $P < 0.001$), this effect was no longer statistically significant at month 6. The reduction in mean OCT central subfield retinal thickness was greater in the 0.7 mg ($208 \pm 201 \mu\text{m}$) and 0.35 mg ($177 \pm 197 \mu\text{m}$) groups than in the sham group ($85 \pm 173 \mu\text{m}$) at month 3 ($P < 0.001$), but not statistically significant at month 6.

Currently, there is no randomized controlled trial comparing anti-VEGF agents and Ozurdex[®] directly. At 12 months, Campochiaro et al determined that with monthly treatment of ranibizumab in the first 6-month period and then as needed treatment in the second 6 month period, mean change in VA from baseline for patients with BRVO was +7.3, +16.6, and +18.3 letters for control, 0.3 mg ranibizumab, and 0.5 mg ranibizumab, respectively.¹³ At 12 months, Brown et al found that with monthly treatment of ranibizumab in the first 6 month period and then as needed treatment in the second 6 month period, mean change in VA from baseline for patients with CRVO was +0.8, +12.7, and +14.9 letters for control, 0.3 mg ranibizumab, and 0.5 mg ranibizumab, respectively.¹⁴ A disadvantage to anti-VEGF treatment is the need for frequent injections.

In patients with BRVO treated with Ozurdex[®], mean change in VA from baseline was approximately +6.6 letters for retreated patients and +6.5 letters for delayed treatment. In patients with CRVO treated with Ozurdex[®], mean change in VA from baseline was approximately +2.2 letters for retreated patients and -1.2 letters for delayed treatment.

Safety and tolerability of the Ozurdex® implant

The safety and tolerability of a sustained-release implant are particularly important due to the long duration of exposure to the drug and the drug vehicle, in some cases up to 6 months. In addition, the relative difficulty of explantation makes the recognition of any and all associated serious adverse events paramount. The safety of the implant may be divided into several categories: complications arising from the implantation procedure; toxicity or immunoreactivity associated with exposure to the implant polymer; and toxicity associated with exposure to the agent itself, both in the immediate and long term. In addition, the rate of drug release from the implant is crucial to maintaining the concentration of drug inside the eye and at the vitreoretinal interface within the safe therapeutic window.

Patient intolerance of an implantable drug delivery device may be associated with symptomatic local or systemic toxicity of either the drug or the implant vehicle; the implantation procedure, including local irritation or reaction at the implantation site; or even anxiety and other psychological stress with regard to the invasive nature of the procedure.

Polymer toxicity

The DEX intravitreal implant is composed of a biodegradable co-polymer of lactic acid and glycolic acid impregnated with a variable dose of DEX. The use of this co-polymer for slow release drug delivery was initially described over 30 years ago for a variety of applications, including antimalarial drugs, contraception, and anesthetics. Multiple *in vitro* and *in vivo* studies have confirmed its biocompatibility.^{15,16} Intramuscular implantation results in a mild foreign body reaction similar to the degree seen in response to synthetic suture material, while *in vivo* studies of intravitreal implantation show virtually no ocular toxicity.^{16,17}

Dexamethasone toxicity

Early animal studies determined that a high concentration of DEX could be achieved intravitreally without any clinical, histological, or electrophysiological toxicity. Kwak and D'Amico found increasing levels of retinal toxicity occurring at doses above 800 µg administered to rabbits; however, another study found that up to 4.8 mg of DEX was tolerated intravitreally with no adverse consequences.^{18,19} Another animal study of a poly (lactide-co-glycolide) DEX implant found that the intraocular DEX concentration was constant over time, and that electroretinographic studies confirmed no change in normal retinal physiology.¹⁸

Clinical trials

An early trial of the DEX implant compared 0.35 mg and 0.7 mg doses to a noninjection observation group for the treatment of macular edema of various etiologies. In the study, a number of ocular adverse events occurred in each of the treatment groups, including anterior chamber cell and flare, vitreous hemorrhage, and ocular pain or irritation. The majority of these events occurred within the first 7 days after injection, and the only events that occurred at a significantly higher rate after this period were anterior chamber flare (5%) and elevated intraocular pressure (6%), both occurring in the 0.7 mg group only. Intraocular pressure increases of greater than 10 mmHg or to an absolute level of 25 mmHg occurred in less than 20% of each DEX group, and all instances of ocular hypertension were managed medically. The rate of cataract formation was not significantly higher in either treatment group than in the observation group throughout the 180-day study period.²⁰

Several adverse events were believed to be related to traumatic implantation; thus, a subsequent study compared the safety profile of surgical implantation with that of a novel proprietary applicator device.²¹ Use of the applicator device was associated with a lower overall incidence of ocular adverse events (68.4% vs 90%), although this difference was not statistically significant. Of note, there were no reports of vitreous hemorrhage in the applicator group, compared with 2 out of 10 patients in the incisional group who experienced this complication. However, the study was insufficiently powered to determine a statistically significant difference for this or any other infrequently occurring adverse event.

The largest published clinical trial of the DEX implant to date has compared visual, anatomic, and safety outcomes over 6 months in patients with macular edema from central or branch retinal vein occlusion. The overall incidence of ocular adverse events was comparable to previous studies, at a rate of 62.9% in the 0.7 mg group and 61.9% in the 0.35 mg group. This was significantly higher than the rate of 42.8% in the sham procedure group.²¹ Only 3 specific events (eye pain, ocular hypertension, and anterior chamber cellular reaction) occurred at a significantly higher rate than in the sham group. Although the incidence of ocular hypertension was higher in the treatment groups, the vast majority of cases were transient instances of elevated intraocular pressure, which were managed either by observation or with topical medications alone. Intraocular pressure typically reached a peak at 2 months, decreasing steadily over the next 4 months. At this peak time point, the authors reported that 16% of all patients had a pressure of greater than 25 mmHg. Of note, the

proportion of patients using ocular antihypertensive agents increased from 6% at study entry to 24% at 6 months among all patients in the treatment group. An increase of at least 10 mmHg from baseline was seen in 12.6% of study eyes at 2 months after the first DEX implant and 15.4% of study eyes at 2 months after the second DEX implant.¹² Over the total 12-month study period, 32.8% of retreated DEX 0.7/0.7 patients had at least a 10 mmHg increase from baseline at some point over the 12-month period. Ultimately, fourteen eyes required laser or surgery to reduce intraocular pressure. The rate of cataract formation was not significantly different in any treatment group than in the sham group during the first 6 months. However, over the 12-month study period, cataracts were reported in 29.8% of phakic study eyes in the retreated DEX 0.7/0.7 group, 19.8% of the DEX 0.35/0.7 group, and 10.5% of the delayed treatment (sham/0.7) group ($P = 0.001$). Eleven patients underwent cataract surgery (unpublished data).

Quality of life measures

Among the most important factors in determining patient perception of a treatment modality is a risk–benefit analysis, in which the potential effectiveness of a treatment is weighed against the probability, severity, and treatability of adverse events. Additionally, patient perceptions of the disease process and its likely prognosis with and without treatment are likely to influence a patient's choice to proceed with treatment. Finally, the invasiveness and perceived discomfort of the treatment can be a significant factor in the decision-making process.

Although central and branch vein occlusions occur frequently, only a few studies have objectively examined their impact on patient quality of life. Awdeh et al and Deramo et al examined the vision-related quality of life indices in patients with branch and central retinal vein occlusions, respectively, using the National Eye Institute Visual Function Questionnaire (VFQ-25). Each found significantly lower scores than a normal reference group in almost all subscales, including areas such as general health, driving and reading vision, dependency, social functioning, and mental health.^{22,23} Additionally, Chang et al surveyed patients with macular edema resulting from vein occlusion in order to determine a vision preference value (a value validated in patients with age-related macular degeneration), and found similar values to those patients with subfoveal choroidal neovascularization. They also found that greater than two-thirds of these patients showed some enthusiasm for intravitreal injection in order to improve vision, despite

the somewhat invasive nature of the procedure, suggesting a significant impact of the diseases on visual functioning.²⁴ We may speculate that patients with vein occlusion might also express enthusiasm in other relatively invasive treatments such as the DEX intravitreal implant.

Place in therapy and conclusion

In the recent phase III trial that randomized the DEX implant against a sham treatment, the DEX implant demonstrated short term clinical efficacy by several metrics, including the percentage of patients achieving a 10- to 15-letter improvement in vision; the rate at which patients achieved visual improvement; the mean improvement in vision; and central macular subfield thickness as measured by OCT. At 6 months, however, the proportion of patients achieving a 15-letter improvement (a primary outcome measure in the study) was no longer significantly higher than sham. Subgroup analyses of CRVO and BRVO showed a similar pattern, with the peak effect as measured by mean change in vision and proportion of patients improved occurring at study month 2 with a reduction in effect through month 6.

By comparison, we may refer to recent data comparing intravitreal TA to the standard of care for the treatment of macular edema secondary to branch and central retinal vein occlusion (SCORE study).^{5,6} For the treatment of BRVO, respectively 25.6% and 27.2% of patients receiving 1-mg and 4-mg doses of TA at 4-month intervals improved 15 letters in the first year, compared with 28.9% in the grid laser group. These values are comparable to the month 2 results in BRVO arm of the DEX implant study, in which 30% and 26% of eyes in the 0.7 mg and 0.35 mg groups, respectively, showed a 15-letter improvement. However, patients in this study were eligible to be retreated with laser or triamcinolone prior to the 6-month time point, which was not permitted in the Ozurdex study, to some extent limiting direct comparison. Similarly, TA for the treatment of CRVO resulted in 25.6% and 26.5% of patients in the 1-mg and 4-mg groups improving 15 letters in the first year, compared with 6.8% of patients in the standard of care (observation) group. This was also comparable to the DEX implant study group, in which 29% and 33% of patients in the 0.7 mg and 0.35 mg groups, who experienced the same increase in vision at the peak response time of 2 months post implantation. In each of the TA groups, patients received an average of 2 injections in the first year.

Adverse events occurring in the SCORE study included increase in intraocular pressure necessitating initiation of pressure-lowering medication; progressive lens opacity; and minor adverse events including conjunctival hemorrhage and

vitreous floaters. Although the rates of elevated IOP (up to 41%) and progressive lens opacity (up to 35%) were significantly higher in the SCORE study than in patients receiving the DEX implant, these results, as well as those showing clinical efficacy, should be compared with caution, in the absence of direct randomized, comparative controlled trials.

Ranibizumab has also been used with success in the treatment of macular edema associated with both BRVO and CRVO. The recently published BRAVO and CRUISE studies showed a significant proportion of patients achieving a 15-letter improvement with an average of almost one injection per month. For BRVO, 55.2% and 61.1% of patients receiving 0.3 mg and 0.5 mg of ranibizumab achieved this outcome by 6 months.²⁵ For CRVO, 15 or more letters were gained by 46.2% and 47.7%, respectively.²⁶ Central macular thickness as measured by OCT showed a corresponding decrease, while the occurrence of adverse events was not significantly different from the sham injection group of either study. Again, in the absence of a randomized, clinical trial comparing these treatments, direct comparisons between these studies and the DEX implant studies should only be made with caution.

The DEX implant has two potential advantages over other therapies currently employed for macular edema secondary to vein occlusion. The continuous release of medication maintains a consistent level of the drug within the eye over an extended period, eliminating the need for monthly or bimonthly injections, as might be necessary with intravitreal anti-VEGF agents. Additionally, the sustained release formulation provides the potency of DEX while compensating for the short intraocular half-life of the medication.

Still undetermined, however, are long-term adverse events associated with the implantation, including the incidence of cataract and glaucoma. Increased intraocular pressure was certainly noted in more than one study, although at 6 months, did not approach the level seen with the use of TA in the SCORE study. Cataract formation at 6 months was negligible; however, the authors of the DEX implant phase III trial have recognized that the initial study period may be insufficient to demonstrate significant progression of lens opacity. Indeed, as-yet unpublished 12-month data suggest that the DEX implant does increase the risk of cataract.

In summary, the DEX intravitreal implant is a minimally invasive treatment modality that has shown initial clinical efficacy in the treatment of macular edema resulting from retinal vein occlusion. Randomized clinical trials have shown that, in the short term, it improves vision, as well as decreases the risk of vision loss after a single intervention. However, most patients may ultimately still attain only a modest or temporary, though

measurable, improvement in vision with a single injection, and repeat injection is usually necessary for most CRVO patients. That does not appear to be the case for BRVO patients where the natural history, as well as treatment outcomes, appears more favorable. Thus, the DEX implant is an additional pharmacologic agent in our arsenal. It may be most appropriate for motivated, phakic, or pseudophakic patients with simple branch retinal vein occlusions associated with macular edema and significant hemorrhage, who are unwilling or unable to tolerate more frequent intravitreal injections required for anti-VEGF therapy, or for patients who have demonstrated intolerance or recalcitrant edema following anti-VEGF therapy. It may also be a suitable choice for patients with CRVO, particularly those who are already pseudophakic and not steroid responders, and who are not good candidates for anti-VEGF agents for other reasons such as intolerance or pre-existing thromboembolic disease. For patients with only a minimal response to the DEX implant, monotherapy with additional implants would not be recommended. Some consideration might be given to combination therapy with both an anti-VEGF agent and DEX or TA. If, after discussion, the patient and physician prefer a steroid agent to anti-VEGF therapy, intravitreal TA is a reasonable, but shorter acting alternative, and has also been shown to exhibit prolonged bioavailability in the eye. Beer et al performed the first human study to determine intravitreal TA concentration by measuring aqueous samples after a single 4 mg intravitreal TA injection. They found the half-life in nonvitrectomized eyes to be 18.6 days and estimated that TA can be present in the eye for up to 3 months after injection.²⁷ Mason et al studied both the aqueous and vitreous concentrations after intravitreal TA injection in 6 eyes and also found detectable levels in patients sampled approximately 3 months from the time of injection.²⁸ Although the sample size was small in both studies, they are consistent with other small clinical results and our own clinical observations. The smaller gauge needle and significantly smaller cost of TA may be preferable to some physicians and patients but not others. Further study, including randomized trials comparing the DEX implant to grid laser in BRVO, intravitreal anti-VEGF agents, and triamcinolone, are anticipated to help clarify some of these issues.

Disclosure

None of the authors have a direct proprietary interest in any of the products used in this study. Dr Blumenkranz has served as a consultant to Allergan, the manufacturer of Ozurdex, and the Triamcinolone formulation for the SCORE Study. He has also been a consultant to Genentech, the manufacturer of ranibizumab and bevacizumab.

References

- Rogers S, McIntosh RL, Journ GD, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:313–319.
- The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol*. 1984;98:271–282.
- The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion: the Central Vein Occlusion Study Group M report. *Ophthalmology* 1995;102:1425–1433.
- Leopold IH. Nonsteroidal and steroidal anti-inflammatory agents. In: Sears MI, Tarkkanen A, editors. *Surgical Pharmacology of the Eye*. New York: Raven Press, 1985:83–133.
- Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch Ophthalmol*. 2009;127:1101–1114.
- Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol*. 2009;127:1115–1128.
- Edelman JL. Differentiating intraocular glucocorticoids. *Ophthalmologica*. 2010;224(Suppl 1):25–30.
- Gan IM, Ugahary LC, van Dissel JT, van Meurs JC. Effect of intravitreal dexamethasone on vitreous vancomycin concentrations in patients with suspected postoperative bacterial endophthalmitis. *Graefes Arch Clin Exp Ophthalmol*. 2005;243:1186–1189.
- Chang-Lin JE, Attar M, Acheampong AA. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest Ophthalmol Vis Sci*. 2011;52:80–86.
- Kuno N, Fujii S. Biodegradable intraocular therapies for retinal disorders: progress to date. *Drugs Aging*. 2010;27:117–134.
- Yasukawa T, Ogura Y, Tabata Y, Kimura H, Wiedemann P, Honda Y. Drug delivery systems for vitreoretinal diseases. *Prog Retin Eye Res*. 2004;23:253–281.
- Haller JA, Bandello F, Belfort R, et al. Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema Due to Retinal Vein Occlusion. *Ophthalmol*. 2010;117:1134–1146.
- Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion. *Ophthalmology*. 2010;117:1102–1112.
- Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion. *Ophthalmology*. 2010;117:1124–1133.
- Visscher GE, Robison RL, Maulding HV, et al. Biodegradation of and tissue reaction to 50:50 poly(DL-lactide-co-glycolide) microcapsules. *J Biomed Mater Res*. 1985;19:349–365.
- Moritera T, Ogura Y, Honda Y, et al. Microspheres of biodegradable polymers as a drug-delivery system in the vitreous. *Invest Ophthalmol Vis Sci*. 1991;32:1785–1790.
- Fialho SL, Rego MB, Siqueira RC, et al. Safety and pharmacokinetics of an intravitreal biodegradable implant of dexamethasone acetate in rabbit eyes. *Curr Eye Res*. 2006;31:525–534.
- Nabih M, Peyman GA, Tawakol ME, Naguib K. Toxicity of high-dose intravitreal dexamethasone. *Int Ophthalmol*. 1991;15:233–235.
- Kwak HW, D'Amico DJ. Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection. *Arch Ophthalmol*. 1992;110:259–266.
- Kuppermann BD, Blumenkranz MS, Haller JA, et al. Randomized controlled study of an intravitreal dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol*. 2007;125:309–317.
- Haller JA, Dugel DV, Weinberg DV, et al. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. *Retina*. 2009;29:46–51.
- Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2003;121:1297–1302.
- Awdeh RM, Elsing SH, Deramo VA, et al. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. *Br J Ophthalmol*. 2010;94:319–323.
- Chang MA, Fine HF, Bass E, et al. Patients' preferences in choosing therapy for retinal vein occlusions. *Retina*. 2007;27:789–797.
- Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;117:1102e1–1112e1.
- Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;117:1124e1–1133e1.
- Beer PM, Bakri SJ, Singh RJ, et al. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology*. 2003;110:681–686.
- Mason JO, Somaiya MD, Singh RJ. Intravitreal concentration and clearance of triamcinolone acetonide in nonvitrectomized human eyes. *Retina*. 2004;24:900–904.

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