

Pharmacokinetics of a Sustained-Release Dexamethasone Intravitreal Implant in Vitrectomized and Nonvitrectomized Eyes

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PURPOSE. To evaluate dexamethasone pharmacokinetics after implantation of a sustained-release dexamethasone (DEX) intravitreal implant in nonvitrectomized and vitrectomized eyes.

METHODS. The right eyes of 25 rabbits underwent vitrectomy; contralateral eyes served as nonvitrectomy controls. The 0.7-mg DEX implant was injected into both eyes, and drug concentrations were determined in the vitreous humor and retina for 31 days (on days 2, 8, 15, 22, and 31).

RESULTS. DEX was present in nonvitrectomized and vitrectomized eyes for at least 31 days. There were no statistically significant differences in DEX concentration between nonvitrectomized and vitrectomized eyes at any time point ($P > 0.05$). The maximum concentration of DEX in nonvitrectomized versus vitrectomized eyes for vitreous humor was 791 ng/mL (day 22) versus 731 ng/mL (day 22), respectively, and for retina it was 4110 ng/mL (day 15) versus 3670 ng/mL (day 22), respectively. Mean absorption ($AUC_{0-t_{last}}$) of dexamethasone in nonvitrectomized and vitrectomized eyes was not different for both the vitreous humor (13,600 vs. 15,000 ng/day/mL; $P = 0.73$) and retina (67,600 vs. 50,200 ng/day/mL; $P = 0.47$).

CONCLUSIONS. The vitreoretinal pharmacokinetic profiles were similar between nonvitrectomized and vitrectomized eyes. These observations are consistent with clinical findings of the DEX implant in patients who have undergone vitrectomy and should reduce concerns about the use of the DEX implant in eyes that have undergone vitrectomy. (*Invest Ophthalmol Vis Sci.* 2011;52:4605–4609) DOI:10.1167/iovs.10-6387

Vitrectomy is a mainstay of treatment for the severe complications associated with persistent posterior segment disease.^{1–4} However, for many patients, the chronic and recurrent nature of posterior segment disease necessitates continued drug therapy after surgery.^{1,2,4} Experience with vascular endothelial growth factor (VEGF)⁵ and a number of drugs,

including triamcinolone acetonide,^{6,7} amphotericin B,⁸ and 5-fluorouracil,⁹ suggests that some drugs are cleared more rapidly in vitrectomized eyes. Therefore, differences in pharmacokinetics between nonvitrectomized and vitrectomized eyes may influence the clinical effectiveness of drug therapy. Intravitreal clearance of drugs intended for the treatment of posterior segment disease should be established in vitrectomized eyes before intravitreal dosing is considered in these patients.

Intravitreal delivery of corticosteroids^{10–17} and anti-VEGF antibodies^{18–22} are addressing many of the problems associated with conventional therapies for the treatment of posterior-segment inflammation and macular edema. The dexamethasone (DEX) implant (Ozurdex; Allergan, Inc., Irvine, CA) is a sustained-release preparation of DEX embedded in a bioerodible copolymer consisting of poly(lactic-co-glycolic acid) that has been approved by the United States Food and Drug Administration (FDA) for the intravitreal treatment of macular edema after branch or central retinal vein occlusion.²³ Pharmacokinetic and pharmacodynamic data suggest that when injected into the posterior segment, the DEX implant releases DEX into the vitreoretinal tissues for up to 6 months.²⁴ Moreover, clinical trials in patients with persistent macular edema have shown that the DEX implant is well tolerated and results in improved visual acuity that is maintained for up to 180 days after administration.^{13,25–27}

Although some information is available on the pharmacokinetics of DEX in the vitreous,^{14,28–30} the effect of vitrectomy on the pharmacokinetics of the DEX implant has not been examined. The objective of this study was to compare the ocular pharmacokinetics and in vivo drug release profile of the DEX implant in nonvitrectomized and vitrectomized eyes.

METHODS

Animal Model and Study Design

The study complied with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and was conducted in accordance with the FDA Good Laboratory Practice Regulations and applicable Animal Welfare Act Regulations. The study was approved by Allergan's Animal Care and Use Committee.

The study used young, male, Dutch-belted rabbits weighing 1.8 to 2.5 kg that were 5 to 12 months old. Animals were maintained in a temperature- and humidity-controlled environment with a 12-hour day/12-hour night cycle. Standard rabbit feed and purified water were offered ad libitum.

A single-treatment design was used, with one treatment group and terminal samples from each animal at necropsy. The right eyes of 25 animals underwent vitrectomy; left eyes did not. Four weeks after vitrectomy, a single bilateral intravitreal implantation of the DEX-DDS

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was made into both eyes. Ocular tissue samples were collected at necropsy on days 2, 8, 15, 22 and 31 after implantation (five animals per time point).

Animals were examined daily for morbidity and mortality. The intraocular pressure (IOP) of both eyes of each animal was measured before vitrectomy, 2 weeks after vitrectomy, once weekly after administration of the DEX implant, and before necropsy. IOP was measured at approximately the same time of day after the administration of an ophthalmic topical anesthetic (0.5% proparacaine hydrochloride; Wilson Ophthalmic Corp., Mustang, OK).

Vitrectomy

Animals were anesthetized with intravenous 15 mg/kg ketamine hydrochloride (Ketaset; Fort Dodge Animal Health, Fort Dodge, IA) and 1 mg/kg acepromazine maleate (Prom Ace; Fort Dodge Animal Health). The right eyes of 25 animals were prepared for vitrectomy with 2.5% phenylephrine hydrochloride (AK-Dilate; Akorn Inc., Buffalo Grove, IL) and 1% tropicamide ophthalmic solution (Alcon Laboratories, Fort Worth, TX) and were washed with 5% povidone iodine solution (Betadine 5% sterile ophthalmic prep solution; Alcon Laboratories). Animals underwent vitrectomy as follows: the eye was proptosed, and two ports of vitrectomy were marked 4 mm behind the corneal limbus. A trocar with a 25-gauge port was inserted into the vitreous at each mark through a short sclerotic tunnel. The infusion cannula was connected to a bottle of sterile balanced salt solution. A near complete subtotal vitrectomy was performed with an 1100 to 1500/min cutter rate and 300 to 600 mm Hg aspiration pressure for 10 to 12 minutes per eye. The vitreous cavity was filled with the sterile balanced salt solution, the trocars were removed, and topical antibiotic and 1% atropine sulfate ophthalmic solution (Bausch & Lomb, Tampa, FL) were applied to the conjunctival sac. The topical antibiotic and atropine were also applied for 3 days after surgery. The contralateral (left) eye was not vitrectomized.

Intravitreal Administration Procedure

Four weeks after vitrectomy, animals received a single, administration of 0.7 mg DEX. Animals were anesthetized with ketamine hydrochloride and acepromazine maleate, as described, and 0.5% proparacaine hydrochloride ophthalmic drops (Wilson Ophthalmic Corp., Mustang, OK) were applied topically. The eyes were prepared for administration of the DEX implant with 5% povidone iodine (Betadine 5% sterile ophthalmic prep solution; Alcon Laboratories) followed by sterile balanced salt solution. A 22-gauge needle of a preloaded DEX implant applicator was introduced through the dorso-temporal quadrant of the eye, approximately 4 mm posterior to the limbus. The DEX implant was deployed in the inferior temporal region of the vitreous using the single-use applicator. Topical antibiotic was applied after the procedure. The location of the DEX implant was confirmed by funduscopy, Heidelberg retina angiograph examination, or both.

Tissue Collection and Handling

Animals were euthanized with an intravenous injection of pentobarbital sodium (Eutha-6; Western Medical Supply, Arcadia, CA). Both globes were enucleated and immediately frozen in liquid nitrogen. After the cornea, iris, ciliary body, and lens were excised, the globes were bisected transversely into two hemispheres, one with the DEX implant and one without the DEX implant. Care was taken to ensure that the sample without the DEX implant was not contaminated with implant remnants during dissection, and instruments were cleaned (with alcohol followed by distilled water) between samples to ensure that there was no cross contamination during dissection. Retina was dissected from both hemispheres (i.e., with and without the DEX implant) and was analyzed separately. Samples were stored at -20°C or lower until analyzed.

Drug Determination

The concentration of DEX in the total retina (nanogram per gram) was calculated by dividing the total amount of DEX from retinal samples

dissected from both hemispheres by the total tissue weight. The concentration of DEX was analyzed separately for the vitreous humor. Only data for the vitreous humor hemispheres without the implant are reported because these data describe the concentration of soluble DEX released from the implants. Data for the vitreous humor hemispheres with the implant were not reported.

Liquid-liquid extraction was used to extract DEX from the samples, as described previously.²⁴ Briefly, the internal standard, beclomethasone, was added to the retina and vitreous humor samples, and the organic phase was separated by liquid extraction with 95% methanol/5% water (retina samples) or methyl tert butyl ether (vitreous humor samples). Dried residues were reconstituted with 70% methanol/30% water with 0.1% acetic acid. DEX concentrations in the reconstituted samples were determined by LC-MS/MS using triple quadrupole mass spectrometers (API 3000 and API 4000; Applied Biosystems/SCIEX, Concord, ON, Canada). The mass spectrometers were interfaced with a high-performance liquid chromatography system (Shimadzu, Columbia, MD) and an autosampler (Leap Technologies, Carrboro, NC). High-performance liquid chromatography was conducted on a column (3.9×150 mm, $4 \mu\text{m}$) (Novapak C18; Waters Corporation, Milford, MA), using 85:15 methanol/0.1% aqueous acetic acid as the mobile phase. Mass spectrometry data were detected using positive ionization with heated nebulizer sources (electrospray ionization or atomic pressure chemical ionization) and scanning in the multiple reaction monitoring mode. The specific precursor product ion pairs used were m/z 393 \rightarrow m/z 373 (DEX) and m/z 409 \rightarrow m/z 391 (beclomethasone). The retention time of DEX and the internal standard was approximately 1.5 minutes.

Linear assay ranges were as follows: vitreous humor, 0.500 to 1000 ng/mL; retina, 0.100 to 100 ng per sample. Precision (percentage coefficient of variation) for quality control samples was less than 15%. Accuracy was within $\pm 15\%$ of the nominal value for vitreous humor samples and was within $\pm 20\%$ for retinal samples.

Pharmacokinetic Analysis

DEX pharmacokinetic data were analyzed using a noncompartmentalized model in a Watson laboratory information system, version 6.3 (Thermo Electron Corporation, Waltham, MA). The following parameters were calculated: maximum mean concentration (C_{max}), time to reach maximum mean concentration (T_{max}), area under the concentration-time curve ($\text{AUC}_{0-\text{last}}$), and AUC interval.

The content of the DEX implant batch used in this study consisted of 678,000 ng DEX and 22,000 ng polymer. The percentage of drug remaining in the DEX implant at day 31 was determined by dividing the amount of DEX in the vitreous humor with implant samples by the total DEX content of the implant (678,000 ng).

Statistical Analysis

Data were analyzed using the Watson laboratory information system, version 6.3. Sample concentrations and pharmacokinetic data were described by means \pm SD except for $\text{AUC}_{0-\text{last}}$, for which the mean \pm SEM was used. Outliers in repetitive measurements were identified using the Q-test.³¹ Differences between nonvitrectomized and vitrectomized eyes were determined using the paired Student *t*-test; $P < 0.05$ was considered significant.

RESULTS

Clinical Observations

All animals appeared physically healthy and exhibited no overt signs of toxicity during the study, and none died. The location of the implants in the 25 nonvitrectomized and 25 vitrectomized eyes was confirmed by funduscopy before necropsy or Heidelberg retina angiography. Generally, implants were observed in their original position in the inferior temporal region.

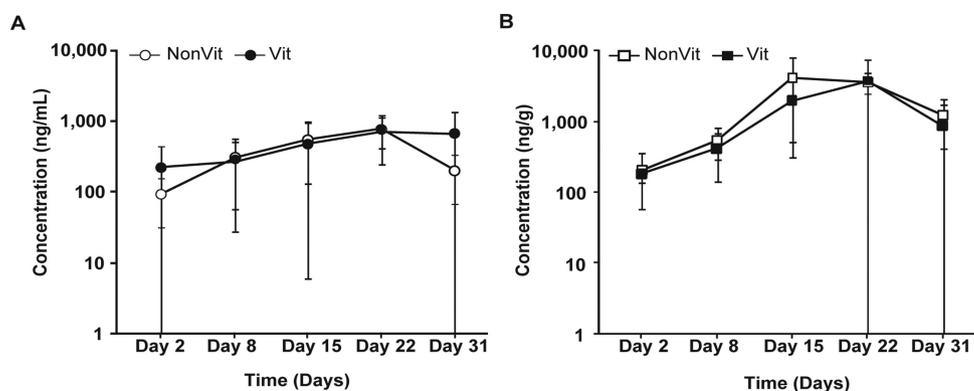


FIGURE 1. Concentration of DEX (mean \pm SD) in the (A) vitreous humor and (B) retina after administration of the DEX implant in nonvitrectomized (NonVit) and vitrectomized (Vit) eyes. Differences between Non-Vit and Vit eyes at each visit were not statistically significant ($P > 0.05$).

Ocular Concentrations and Pharmacokinetic Profiles

Sustained release of DEX was evidenced by high intraocular concentrations of steroid that were maintained for at least 31 days in the vitreous humor and retinas of both nonvitrectomized and vitrectomized eyes (Fig. 1). Overall, there were no statistically significant differences in the concentration of DEX between nonvitrectomized and vitrectomized eyes for either tissue at any time point (Table 1). As expected, the mean maximum concentration of DEX was approximately fivefold higher in the retina than in the vitreous humor (Table 2) and was similar between nonvitrectomized and vitrectomized eyes for the retina (4110 ng/g vs. 3670 ng/g, respectively) and for the vitreous humor (791 ng/mL vs. 731 ng/mL, respectively). The mean T_{max} was the same in the vitreous humor of nonvitrectomized and vitrectomized eyes and in the retinas of vitrectomized eyes (22 days). Mean T_{max} was slightly shorter in the retinas of nonvitrectomized eyes (15 days). There were no significant differences in the absorption (AUC_{0-31}) of DEX between nonvitrectomized and vitrectomized eyes for both the vitreous humor (13,600 ng \cdot days/mL vs. 15,000 ng \cdot days/mL; $P = 0.73$) and the retina (67,600 ng \cdot days/g vs. 50,200 ng \cdot days/g; $P = 0.47$; Table 2).

Release of DEX from the DEX Implant

By day 31, the percentage of DEX remaining in the implant was similar in nonvitrectomized ($5.0\% \pm 3.3\%$) and vitrectomized ($4.2\% \pm 5.4\%$) eyes.

DISCUSSION

In this study, we have demonstrated similar vitreoretinal DEX pharmacokinetics after administration of the 0.7-mg DEX implant in nonvitrectomized and vitrectomized eyes. The concentration-time profiles for DEX were congruent for nonvitrectomized and vitrectomized eyes for both vitreous humor and

retina for the duration of the study. Overall, our findings should reduce concerns with the use of the DEX implant in the eyes of patients who have undergone vitrectomy.

After vitrectomy, the vitreous is often replaced with an aqueous saline solution of lower viscosity than the normal vitreous humor. In vitro data suggest that DEX diffuses more quickly through saline solutions than normal vitreous humor.³² Moreover, an earlier study¹⁴ examining the in vivo release of DEX sodium m-sulfobenzoate from a biodegradable poly(lactic acid) (PLA) implant suggests that the pharmacokinetics of DEX may be different in nonvitrectomized and vitrectomized eyes. In this earlier study conducted in rabbit eyes, the release of DEX from the PLA implant (which has chemical similarities with the DEX implant) was 2.5 times more rapid in vitrectomized eyes than in nonvitrectomized eyes. In contrast, the release of DEX from the DEX implant in our study was similar between nonvitrectomized and vitrectomized eyes. This suggests that the dissolution rates of sustained-release DEX from the implant were not different between the balanced salt solution used to replace the vitreous humor in vitrectomized rabbit eyes and normal vitreous humor. Further, assessment of the PLA implant found a good correlation between in vitro and in vivo release for vitrectomized eyes but not for nonvitrectomized eyes. This finding suggests that DEX release from the PLA implant depended on the physicochemical properties of the milieu, with more rapid release into aqueous saline buffer, compared with the more viscous vitreous.¹⁴

The anatomic and physiological differences between rabbit eyes and human eyes should be considered when applying the findings of this study to human eyes. Findings from this study suggest that release of drug from the DEX implant is relatively fast (1–2 months) in rabbit eyes compared with, for example, monkey eyes, in which DEX is released from the implant for up to 6 months.²⁴ The factors that can affect drug release from the implant are the implant characteristics (e.g., drug-polymer interactions), the solubility of drug in the vitreous humor, and the proximity of the implant to the primary elimination path-

TABLE 1. Dexamethasone Concentration in the Vitreous Humor and Retina after Administration of the 0.7-mg Dexamethasone Implant in NonVit and Vit Eyes

Day	Vitreous Humor (ng/mL)			Retina (ng/g)		
	NonVit	Vit	<i>P</i>	NonVit	Vit	<i>P</i>
2	95.7 (63.7)	226 (284)	0.47	203 (146)	180 (42.8)	0.78
8	313 (256)	271 (243)	0.91	544 (257)	408 (268)	0.49
15	560 (426)	487 (481)	0.89	4110 (3600)	1940 (1630)	0.33
22	791 (367)	731 (484)	0.80	3620 (1170)	3670 (3780)	0.98
31	203 (135)	687 (980)	0.36	1220 (810)	849 (939)	0.55

Data are mean (SD) for $n = 3$ to 5.

TABLE 2. Pharmacokinetic Parameters of Dexamethasone in the Vitreous Humor and Retina after Administration of the 0.7-mg Dexamethasone Implant in NonVit and Vit Eyes

Parameter	Vitreous Humor		Retina	
	NonVit	Vit	NonVit	Vit
C _{max}	791 (367) ng/mL	731 (484) ng/mL	4110 (3600) ng/g	3670 (3780) ng/g
T _{max} , days	22	22	15	22
AUC _{0-tlast}	13,600 (2270) ng · days/mL	15,000 (3280) ng · days/mL	67,600 (15,400) ng · days/g	50,200 (16,300) ng · days/g
AUC interval, days	0-31	0-31	0-31	0-31

Data are mean (SD) for C_{max} (n = 3 to 5) and mean (SEM) for AUC_{0-tlast}.

way.³³⁻³⁵ Given the lipophilic nature and the relatively low molecular weight of DEX, elimination is largely driven by diffusion through the retina.^{36,37} In rabbit eyes, the implant is placed closer to the retina than in monkey eyes to avoid the large rabbit lens. Therefore, placement of the implant closer to the primary elimination pathway in rabbit eyes may increase the speed at which drug is released from the implant.³⁴ However, once drug is released, factors such as vitreoretinal kinetics and route of elimination govern the rate of drug clearance from the vitreous,³⁶ and the intravitreal half-life of DEX is expected to be similar between different species. Indeed, the estimated half-life of intravitreal DEX phosphate has been reported to be 3.5 hours in healthy rabbit eyes²⁹ and 5.5 hours in patient eyes coadministered DEX and vancomycin for the treatment of endophthalmitis.³⁸ Therefore, based on a vitreous volume of 1.4 mL in rabbit eyes and 4 mL in human eyes, we can estimate that the vitreal clearance of DEX is 8 mL/d in rabbit eyes and 12.1 mL/d in human eyes. These findings suggest that the vitreal clearance of the sustained-release DEX in human eyes is unlikely to be greatly different from the vitreal clearance observed in this study. Moreover, given that greater than 90% of DEX had been released from the DEX implant by day 31, this follow-up time was considered sufficient for determining the effect of vitrectomy on the pharmacokinetics of the DEX implant in rabbit eyes. Although this study was conducted for 1 month, pharmacokinetic data from a 9-month study of the DEX implant in primate eyes suggests that DEX is present at high concentrations in the vitreous humor and retina for up to 60 days and can be maintained for 6 months after administration of the implant.²⁴ These data support the clinical findings of the DEX implant in nonvitrectomized^{13,25-27} eyes of patients with persistent macular edema, in which the DEX implant was well tolerated and provided sustained improvements in visual acuity for 180 days.^{13,25-27} In addition, the sustained release of DEX in the present study was consistent with preliminary clinical evidence from an open-label study³⁹ of the DEX implant in vitrectomized eyes of patients with diabetic macular edema. In this pilot study, statistically significant improvements from baseline in central retinal thickness and visual acuity were observed 6 months after patients received the implant.

Given that the completeness of vitrectomy may influence the rate of clearance of many drugs,⁶ the extent of vitrectomy should be considered when comparing findings between non-vitrectomized and vitrectomized eyes. In our study, a near complete subtotal vitrectomy was performed and the pharmacokinetics of the DEX implant between nonvitrectomized and vitrectomized eyes were similar, which suggests that the extent of vitrectomy was not an important consideration in the interpretation of our results. Moreover, the variation in the concentrations of DEX found in the vitreous humor and retina is unlikely to be a result of differences in the extent of vitrectomy in some eyes and at some time points. Considerable variation in DEX concentrations were observed in both non-

vitrectomized and vitrectomized eyes, and this variation most likely occurred as a result of small implant remnants contaminating the “no implant” vitreous humor fractions or small remnants in some retinal tissue samples. In addition, because all concentrations of DEX measured in the no implant samples in this study were well below the solubility of DEX in water (i.e., 100,000 ng/mL), our findings are likely to reflect differences in the concentration of soluble DEX in the vitreoretinal tissues.

In conclusion, this study has demonstrated similar pharmacokinetics of DEX in nonvitrectomized and vitrectomized eyes after administration of a 0.7-mg DEX implant. These data are relevant because they support the clinical findings that have been reported for the DEX implant in nonvitrectomized and vitrectomized eyes of patients with persistent macular edema.

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References

- Laidlaw DA. Vitrectomy for diabetic macular oedema. *Eye*. 2008; 22(10):1337-1341.
- Androudi S, Ahmed M, Fiore T, Brazitikos P, Foster CS. Combined pars plana vitrectomy and phacoemulsification to restore visual acuity in patients with chronic uveitis. *J Cataract Refract Surg*. 2005;31(3):472-478.
- Parodi MB, Lanzetta P, Guarnaccia G, Friberg T. Surgical treatments of central retinal vein occlusion. *Semin Ophthalmol*. 2003; 18(3):142-146.
- Arrigg PG, Cavallerano J. The role of vitrectomy for diabetic retinopathy. *J Am Optom Assoc*. 1998;69(11):733-740.
- Lee SS, Ghosn C, Yu Z, et al. Vitreous VEGF clearance is increased after vitrectomy. *Invest Ophthalmol Vis Sci*. 2010;51(4):2135-2138.
- Chin HS, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. *Retina*. 2005;25(5):556-560.
- Schindler RH, Chandler D, Thresher R, Machemer R. The clearance of intravitreal triamcinolone acetonide. *Am J Ophthalmol*. 1982; 93(4):415-417.
- Doft BH, Weiskopf J, Nilsson-Ehle I, Wingard LB Jr. Amphotericin clearance in vitrectomized versus nonvitrectomized eyes. *Ophthalmology*. 1985;92(11):1601-1605.
- Jarus G, Blumenkranz M, Hernandez E, Sossi N. Clearance of intravitreal fluorouracil: normal and aphakic vitrectomized eyes. *Ophthalmology*. 1985;92(1):91-96.
- Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results. *Arch Ophthalmol*. 2008; 126(9):1191-1201.

11. Enyedi LB, Pearson PA, Ashton P, Jaffe GJ. An intravitreal device providing sustained release of cyclosporine and dexamethasone. *Curr Eye Res.* 1996;15(5):549-557.
12. Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B, Comstock T. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. *Ophthalmology.* 2006;113(6):1020-1027.
13. 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(3):309-317.
14. Morita Y, Ohtori A, Kimura M, Tojo K. Intravitreal delivery of dexamethasone sodium m-sulfobenzoate from poly(DL-lactic acid) implants. *Biol Pharm Bull.* 1998;21(2):188-190.
15. Silva-Cunha A, Fialho SL, Naud MC, Behar-Cohen F. Poly-epsilon-caprolactone intravitreal devices: an in vivo study. *Invest Ophthalmol Vis Sci.* 2009;50(5):2312-2318.
16. Xu J, Wang Y, Li Y, et al. Inhibitory efficacy of intravitreal dexamethasone acetate-loaded PLGA nanoparticles on choroidal neovascularization in a laser-induced rat model. *J Ocul Pharmacol Ther.* 2007;23(6):527-540.
17. Zhang L, Li Y, Zhang C, Wang Y, Song C. Pharmacokinetics and tolerance study of intravitreal injection of dexamethasone-loaded nanoparticles in rabbits. *Int J Nanomedicine.* 2009;4:175-183.
18. Antoszyk AN, Tuomi L, Chung CY, Singh A. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. *Am J Ophthalmol.* 2008;145(5):862-874.
19. Chakravarthy U, Adamis AP, Cunningham ET Jr, et al. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology.* 2006;113(9):1508 e1501-e1525.
20. Kook D, Wolf A, Kreutzer T, et al. Long-term effect of intravitreal bevacizumab (Avastin) in patients with chronic diffuse diabetic macular edema. *Retina.* 2008;28(8):1053-1060.
21. Singerman LJ, Masonson H, Patel M, et al. Pegaptanib sodium for neovascular age-related macular degeneration: third-year safety results of the VEGF Inhibition Study in Ocular Neovascularisation (VISION) trial. *Br J Ophthalmol.* 2008;92(12):1606-1611.
22. Yeh PT, Yang CM, Lin YC, Chen MS, Yang CH. Bevacizumab pretreatment in vitrectomy with silicone oil for severe diabetic retinopathy. *Retina.* 2009;29(6):768-774.
23. Ozurdex [package insert]. Irvine, CA: Allergan, Inc.; 2010.
24. Chang-Lin E, Attar M, Acheampong A, et al. Pharmacokinetics and pharmacodynamics of the sustained-release dexamethasone intravitreal implant. *Invest Ophthalmol Vis Sci.* 2011;52(1):80-86.
25. Haller JA, Bandello F, Belfort R Jr, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology.* 2010;117(6):1134-1146.e3.
26. Haller JA, Dugel P, Weinberg DV, Chou C, Whitcup SM. 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(1):46-51.
27. Williams GA, Haller JA, Kuppermann BD, et al. Dexamethasone posterior-segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine-Gass syndrome. *Am J Ophthalmol.* 2009;147(6):1048-1054. e1-2.
28. 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(6):525-534.
29. Kwak HW, D'Amico DJ. Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection. *Arch Ophthalmol.* 1992;110(2):259-266.
30. Weijtens O, Feron EJ, Schoemaker RC, et al. High concentration of dexamethasone in aqueous and vitreous after subconjunctival injection. *Am J Ophthalmol.* 1999;128(2):192-197.
31. Rorabacher D. Statistical treatment for rejection of deviant values: critical values of Dixon's "Q" parameter and related subrange ratios at the 95% confidence level. *Anal Chem.* 1991;63:139-146.
32. Gisladdottir S, Loftsson T, Stefansson E. Diffusion characteristics of vitreous humour and saline solution follow the Stokes Einstein equation. *Graefes Arch Clin Exp Ophthalmol.* 2009;247(12):1677-1684.
33. Friedrich S, Cheng YL, Saville B. Drug distribution in the vitreous humor of the human eye: the effects of intravitreal injection position and volume. *Curr Eye Res.* 1997;16(7):663-669.
34. Chastain J. General considerations in ocular drug delivery. In: Mitra A, ed. *Ophthalmic Drug Delivery Systems*. New York: Marcel Dekker, Inc; 2003:59-107.
35. Yasukawa T, Ogura Y, Tabata Y, Kimura H, Wiedemann P, Honda Y. Drug delivery systems for vitreoretinal diseases. *Prog Retin Eye Res.* 2004;23(3):253-281.
36. Maurice D. Review: practical issues in intravitreal drug delivery. *J Ocul Pharmacol Ther.* 2001;17(4):393-401.
37. Graham RO, Peyman GA. Intravitreal injection of dexamethasone. Treatment of experimentally induced endophthalmitis. *Arch Ophthalmol.* 1974;92(2):149-154.
38. 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(11):1186-1189.
39. Boyer DS, Faber D, Gupta S, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina.* In Press.