

# Phase II Results of an Intraocular Steroid Delivery System for Cataract Surgery

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**Objective:** To evaluate the safety and efficacy of an intraocular biodegradable polymer dexamethasone drug delivery system (DEX DDS) in treating postoperative inflammation after cataract surgery.

**Study Design:** Multicenter, randomized, double-masked, parallel group study comparing two dose levels of the DEX DDS to concurrent placebo and no treatment control subjects.

**Participants:** Ninety patients scheduled to undergo extracapsular cataract extraction with phacoemulsification and intraocular lens implantation participated in the study.

**Intervention:** One or two DEX DDSs, each containing 60  $\mu$ g of dexamethasone, were placed in the posterior chamber after cataract surgery. Patients receiving the placebo received a DDS composed of the same matrix with no active drug. In vivo rabbit studies have determined that the DEX DDS releases dexamethasone into the anterior chamber (AC) for approximately 7 to 10 days.

**Main Outcome Measures:** The AC cells and the AC flare were assessed over a 60-day postoperative period using slit-lamp examination by masked observers. The number and percent of patients in each treatment group requiring additional postoperative topical anti-inflammatory medication were compared.

**Results:** Ninety patients were randomized into 4 treatment groups (30 to the 2 DEX DDS group, 30 to the 1 DEX DDS group, 15 to the placebo DDS group, and 15 to the no treatment group). The control patients required the addition of topical steroids as rescue medication more frequently and sooner than patients receiving DEX DDS (80% vs. 7% at week 2) ( $P < 0.001$ ). Patients receiving DEX DDS showed a significant reduction in postoperative inflammation as assessed by the combined AC cell and flare scores when compared to the control group from day 3 ( $P = 0.002$ ) through week 3. The DEX DDS was well tolerated. No clinically significant difference in any safety evaluations, including intraocular pressure, was seen between the DEX DDS-treated and control groups.

**Conclusion:** The DEX DDS was safe and effective in suppressing postoperative inflammation after uncomplicated cataract surgery. Additional topical anti-inflammatory drops were not needed for most patients.

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Perioperative anti-inflammatory medication for cataract surgery continues to be the standard of care. Untreated or protracted intraocular inflammation may cause increased and prolonged patient discomfort and may contribute to complications such as cystoid macular edema and secondary membrane.<sup>1-3</sup> Corticosteroids are effective in suppressing ocular inflammation and may be administered at the time of surgery via subconjunctival injection, collagen

shield, or eyedrops.<sup>1</sup> Because the therapeutic drug level achieved by these methods is of only short duration, topical steroid is usually continued for several weeks after surgery until the blood-aqueous barrier is re-established.<sup>4,5</sup>

Topical therapy is associated with the well-recognized problems of patient compliance.<sup>6</sup> For many patients, eye-drop instillation poses a significant inconvenience or concern.<sup>7</sup> A variable amount of physician or staff time is needed for patient instruction. For most topical steroids, optimal administration would consist of accurate cul-de-sac instillation, accompanied by punctal closure, of a properly shaken suspension at the appropriate frequency and interval. Even then, poor corneal penetration will limit the level of drug attainable within the anterior chamber (AC).<sup>8</sup>

Oculex Pharmaceuticals (Sunnyvale, CA) has developed an intraocular drug delivery system (DDS) consisting of a biodegradable polymer matrix to which any variety of drugs can be bound. This small, 1-mm-long particle releases the drug continuously as it dissolves. The DDS can be designed so that the duration of drug delivery lasts for periods ranging from days to months.

The first DDS product available for human clinical trials contains 60  $\mu$ g of microdispersed dexamethasone—approximately the same amount of drug contained in a single drop

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of dexamethasone 0.1% ophthalmic solution. Rabbit studies show that after direct placement within the AC, the DEX DDS continuously releases dexamethasone for approximately 7 to 10 days, after which the drug level falls to low or nondetectable levels (Oculex Pharmaceuticals, unpublished data).

The Dexamethasone Drug Delivery System (DEX DDS) has been tested in a phase-I study involving six patients undergoing cataract surgery. The DEX DDS appeared to be effective in reducing postsurgical inflammation, and no clinically significant adverse safety problems related to the DEX DDS were seen. We report the results of a multicenter, randomized, double-masked, placebo-controlled phase-II clinical trial of the DEX DDS for postsurgical inflammation, in which patients received active treatment of one or two DEX DDS. Patients receiving either no treatment or a placebo DDS served as control subjects.

## Patients and Methods

The DEX DDS is a white/off-white rod-shaped filament approximately 0.5 mm in diameter and 1.0 mm in length composed of dexamethasone in a biodegradable polymer matrix. It contains nominally 60  $\mu\text{g}$  of dexamethasone (United States Pharmacopeia). The placebo DDS is identical to the DEX DDS in both appearance and composition of the matrix but contains no dexamethasone.

The protocol and informed consent forms were approved by the Institutional Review Board at each investigational site, and a written informed consent was obtained from participating patients. Male or female patients, at least 21 years old, and who required cataract extraction were eligible for the study. Only one eye per patient was eligible for treatment. Patients with a history of uveitis, concurrent anterior segment disease, or any intraoperative surgical complications were excluded from the study. Disqualifying surgical complications included hemorrhage, wound complications, flat AC, vitreous loss, and either posterior capsule rupture or zonular dehiscence. Ocular or systemic steroidal or nonsteroidal anti-inflammatory medications were not allowed for the 2 weeks before surgery, on the day of surgery, or for the first 2 days after surgery. By postoperative day 3, the masked postoperative examiner could initiate any postoperative anti-inflammatory therapy deemed necessary for ocular inflammation that was failing to improve. Ocular antibiotics were permitted during the perioperative period. Intraoperative or postoperative medications to reduce intraocular pressure (IOP) were also permitted.

After uncomplicated phacoemulsification–intraocular lens surgery, 90 patients at 4 separate investigational sites were randomized in a 2:1 ratio into an active treatment group or a control group. The DEX DDS active treatment group consisted of two equal-sized subgroups in which the patients received either one or two DEX DDSs at the conclusion of surgery. This allowed for comparison of the efficacy of the two different doses. The control group also consisted of two equal-sized subgroups. One subgroup received no treatment at the time of surgery, while the other subgroup received a placebo DDS containing no drug. Patient enrollment and randomization into one of the four subgroups did not occur until the completion of surgery.

After removal of the viscoelastic, the DEX DDS or placebo DDS was inserted by the surgeon into the posterior chamber through the pupil at the 6-o'clock position between the iris and the anterior surface of the intraocular lens. Although the DEX DDS would be effective when placed in the AC, positioning it behind

the iris concealed the DDS from the postoperative slit-lamp examiner. In this manner, the postoperative examiners, who were separate individuals from the surgeons, were masked as to the presence or absence of the DDS. Surgeons were masked as to treatment assignment until the end of surgery. Patients were masked as to the treatment they received until the conclusion of the study.

In addition to a preoperative baseline assessment, patients were examined on postoperative days 1, 3, 7, 14, 21, 30, and 60. Patients requiring further follow-up were seen on day 90. At each study visit, including baseline, an ocular examination was conducted that included best-corrected visual acuity, IOP, slit-lamp examination, and fundus examination. The patient's degree of pain, discomfort, photophobia, and lacrimation were graded. The degrees of conjunctival erythema, ciliary flush, corneal edema, AC cells, and AC flare were graded by slit-lamp examination. The AC cells were graded as: 0 = no cells, 1 = 1 to 5 cells, 2 = 6 to 15 cells, 3 = 16 to 30 cells, 4 = greater than 30 cells, and 5 = hypopyon. The AC flare was graded as: 0 = absent, 1 = trace, 2 = mild intensity, 3 = moderate intensity, and 4 = strong intensity. Any wound problems, iris pathology, adverse events, or concomitant medications were recorded and characterized.

## Statistical Methods

All randomized patients were included in the analysis of efficacy data based on their original assigned treatment group. However, the analysis of safety data was based on patient's actual treatment received during the study. All data analyses were based on the actual observed data. A two-way analysis of variance model, which included treatment, center, and treatment-by-center interaction factors, was used for the analysis of AC cell and AC flare by study visit. Comparisons were made between the active treatment group (one and two DEX DDS subgroups, combined) and the control group (placebo DDS and no treatment subgroups, combined). The least-square mean and its standard error are presented.

For the analysis of the data related to use of rescue medication, the Cochran–Mantel–Haenszel test for general association stratified by center was performed. The Z test for the difference in the proportion of patients without AC cell and flare between active and control groups was performed.

A *t* test for paired data was used for the test of mean change in IOP or in visual acuity from baseline to follow-up visit within treatment group. A two-sample *t* test was used to make comparisons between active and control groups. All statistical tests are two-sided with a 0.05 significance level.

## Results

Ninety patients requiring cataract surgery were randomized in a 2-to-1 ratio into active or control treatment groups at 4 study centers. Thirty patients were assigned to receive 2 DEX DDSs, 30 were assigned to receive 1 DEX DDS, 15 were assigned to receive a placebo DDS, and 15 were assigned to receive no treatment. One patient assigned to receive one DEX DDS actually received no treatment, while another patient assigned to receive a placebo DDS actually received two DEX DDSs. Eighty-nine patients completed the study. One patient who received a single DEX DDS withdrew from the study after the day-1 postoperative visit. Study treatment was unmasked in one patient when two DDSs were seen by the postoperative examiner.

All treatment groups were similar in demographic characteristics and study eye (Table 1). The average age in the study population was 73 years (range, 27–90 years). Among the 90 random-

Table 1. Demographics and Baseline Characteristics

	Treatment Group				Total (n = 90)	P*
	Two DEX DDSs (n = 30)	One DEX DDS (n = 30)	Placebo DDS (n = 15)	No Treatment (n = 15)		
Age (yrs)						0.381
Mean (SD)	72 (11.0)	73 (7.8)	76 (5.4)	70 (10.4)	73 (9.2)	
(Range)	(27, 85)	(47, 90)	(66, 83)	(45, 83)	(27, 90)	
Sex [n (%)]						0.137
Male	10 (33.3)	11 (36.7)	8 (53.3)	10 (66.7)	39 (43.3)	
Female	20 (66.7)	19 (63.3)	7 (46.7)	5 (33.3)	51 (56.7)	
Race [n (%)]						0.698
White	28 (93.3)	24 (80.0)	13 (86.7)	13 (86.7)	78 (86.7)	
Black	0	2 (6.7)	1 (6.7)	1 (6.7)	4 (4.4)	
Asian	2 (6.7)	4 (3.3)	1 (6.7)	1 (6.7)	8 (8.9)	
Treated eye [n (%)]						0.866
OD	18 (60.0)	17 (56.7)	9 (60.0)	7 (46.7)	51 (56.7)	
OS	12 (40.0)	13 (43.3)	6 (40.0)	8 (53.3)	39 (43.3)	

\* P values for the overall comparison among the four treatment groups were based on the F test of the Type III treatment factor from the ANOVA model including only the treatment factor (numerical data) or Fisher's exact test (categorical data).

ized patients, 57% (51 of 90) of the patients were female, 87% (78 of 90) were white, and 57% (51 of 90) had surgery on their right eye. Although 65% (39 of 60) of the patients receiving the DEX DDS were female, compared to 40% (12 of 30) in the control group, this was not a statistically significant difference.

Patients in the control groups (placebo or no treatment) required postoperative topical anti-inflammatory medication for the study eye (rescue medication) more frequently and sooner than did patients receiving DEX DDSs (Table 2). Rescue medications included corticosteroids such as dexamethasone and prednisolone acetate and nonsteroidal anti-inflammatory drugs such as diclofenac. Rescue medication was permitted at day 3 after surgery at the masked examiner's discretion. Forty-seven percent (14 of 30) of the control group patients received a topical anti-inflammatory at day 3 compared to only 3% (2 of 59) of the DEX DDS recipients. By week 2, 80% (24 of 30) of control group patients required a rescue medication compared to 7% (4 of 59) of the DEX DDS group patients. Rescue medication was prescribed for one additional DEX DDS patient at week 3 and for two additional DEX DDS patients at week 4. By the end of the 2-month study, 83% (25 of 30) of the control group patients and 12% (7 of 59) of the DEX DDS-treated patients had used rescue medications. The difference between the DEX DDS patients and the control group patients in use of rescue medications was statistically significant ( $P < 0.001$ ) at every postoperative visit from day 3 on. There was no significant difference in use of rescue medication between the patients who received one or two DEX DDSs or between the patients who received a placebo DDS compared to no treatment.

The AC cells, the AC flare, and the combined sum of AC cell and flare were examined as measures of inflammation. For the majority of visits, there were no statistically significant differences in outcome for those patients receiving one versus those receiving two DEX DDSs (Table 3). There was also no difference between the two control subgroups when these parameters were compared (Table 3). Therefore, efficacy parameters from the combined active treatment groups (one DEX DDS and two DEX DDSs) and the combined control groups (placebo and no treatment) were compared (Table 4).

Mean combined AC cell and flare scores were lower in the DEX DDS group than in the control group from day 3 through month 2. The DEX DDS group showed a statistically significant reduction in postoperative inflammation earlier than the control

group, with mean combined AC cell and flare scores of 2.5 in the DEX DDS group compared to 3.8 in the control group at day 3 ( $P = 0.002$ ) (Table 4). This statistical superiority in effectiveness was maintained at weeks 1, 2, and 3. The greater improvement in the DEX DDS treatment group was seen despite the much higher proportion of patients using a rescue anti-inflammatory medication after day 3 in the control group.

Achievement of a totally quiet AC occurred earlier and more frequently in the DEX DDS-treated patients compared with that of the control patients. Twenty-one percent (12 of 56) of patients receiving one or two DEX DDSs compared to 3% (1 of 30) of patients in the control groups had a combined AC cell and flare score of zero at week 1 ( $P = 0.026$ ) (Table 5). This difference continued through the end of the study, reaching statistical significance at weeks 2 and 3 as well. By the end of the study, 82% (46 of 56) of the DEX DDS recipients had no AC cell or flare compared to 66% (19 of 29) of the control patients ( $P = 0.087$ ), despite the fact that 83% of the control patients had received concomitant anti-inflammatory drops by this time.

Mean AC cell scores alone were consistently lower in the DEX DDS groups than in the control groups from day 3 through month

Table 2. Cumulative Anti-inflammatory Medication Usage for Study Eye by Visit: No. (%) of Patients Who Received Rescue Medication for the Study Eye

	Treatment Group		P*
	Active One and Two DEX DDSs (n = 59)	Control Placebo DDS and No Treatment (n = 30)	
Day 3	2 (3)	14 (47)	<0.001
Week 1	3 (5)	22 (73)	<0.001
Week 2	4 (7)	24 (80)	<0.001
Week 3	5 (9)	25 (83)	<0.001
Month 1	7 (12)	25 (83)	<0.001
Month 2	7 (12)	25 (83)	<0.001

\* P value for the test of treatment effect of categorical outcomes between active and control groups based on the CMH test for general association stratified by center.

Table 3. Analysis of Observed Anterior Chamber Cell and Flare by Treatment Group: Mean (SEM) of Anterior Chamber Cell and Flare Score\*

	Active Groups		P (2 DEX DDSs vs. 1 DEX DDS)	Control Groups		P (placebo DDS vs no treatment)†
	2 DEX DDSs (n = 30)	1 DEX DDS (n = 30)		Placebo DDS (n = 15)	No Treatment (n = 15)	
Day 1	4.0 (0.3)	4.9 (0.3)	0.008	4.1 (0.4)	4.3 (0.4)	0.661
n	29	30		15	15	
Day 3	2.2 (0.3)	2.8 (0.3)	0.228	3.4 (0.4)	4.3 (0.5)	0.197
n	30	28		15	14	
Week 1	1.5 (0.3)	1.2 (0.3)	0.530	2.7 (0.4)	3.6 (0.4)	0.081
n	28	28		15	15	
Week 2	0.9 (0.3)	0.8 (0.3)	0.770	2.2 (0.5)	1.8 (0.5)	0.590
n	28	27		13	13	
Week 3	0.7 (0.2)	0.6 (0.2)	0.826	1.4 (0.3)	1.6 (0.4)	0.766
n	29	27		15	13	
Month 1	0.4 (0.1)	0.3 (0.1)	0.774	0.4 (0.2)	0.7 (0.2)	0.184
n	30	28		15	15	
Month 2	0.3 (0.1)	0.2 (0.1)	0.838	0.5 (0.2)	0.6 (0.2)	0.661
n	30	26		14	15	

\* The mean and SEM (standard error of mean) were estimated from the ANOVA model that includes treatment, center, and treatment-by-center interaction factors.

† P value for the pairwise test of treatment effect of categorical outcomes two groups based on Type III analysis from the model described above.

2. The DEX DDS groups had significantly lower mean AC cells scores than the control groups at day 3 ( $P = 0.022$ ). This statistically significant difference was maintained at weeks 1, 2, and 3.

The AC flare scores alone followed a similar pattern, with mean scores in the DEX DDS groups consistently lower than mean scores in the control groups from day 3 through month 2. A significant difference was seen between the DEX DDS and control groups at day 3 ( $P < 0.001$ ) and at week 1, week 2, and month 1.

The DEX DDS-treated patients had significantly less conjunctival erythema and ciliary flush than did the control patients, beginning at day 1 ( $P < 0.001$  for both parameters) and continuing

through week 2. Significantly less discomfort ( $P < 0.001$ ), pain ( $P = 0.006$ ), photophobia ( $P < 0.001$ ), and lacrimation ( $P = 0.045$ ) were reported by the DEX DDS patients than the control patients at day 3. These statistical differences continued at least through week 1.

The DEX DDS-treated patients showed similar or better outcomes than the control patients for the safety parameters of corneal status (normal/abnormal), corneal edema, fundus status (normal/abnormal), visual acuity, and IOP. Less corneal edema was seen in the DEX DDS-treated patients (49 of 58, 85% with no edema) compared to the control patients (18 of 29, 62% with no edema) beginning at day 3. The difference in the degree of corneal edema was statistically significant at weeks 1 and 2 (both  $P < 0.001$ ).

There was no significant difference between the DEX DDS and control groups in mean change from baseline in visual acuity, with all groups showing significantly improved visual acuity by day 3. Both the DEX DDS and control groups had a mean increase in IOP on day 1 after surgery ( $P < 0.001$  and  $P = 0.002$ , respectively). However, by day 3, both groups had a mean decrease in IOP

Table 4. Analysis of Observed Anterior Chamber Cell and Flare: Mean (SEM) of Anterior Chamber Cell and Flare Score\*

	Treatment Group		P
	Active 1 and 2 DEX DDSs (n = 60)	Control Placebo DDS and No Treatment (n = 30)	
Day 1	4.5 (0.2)	4.2 (0.3)	0.424
n	59	30	
Day 3	2.5 (0.2)	3.8 (0.3)	0.002
n	58	29	
Week 1	1.4 (0.2)	3.2 (0.3)	<0.001
n	56	30	
Week 2	0.9 (0.2)	2.1 (0.4)	0.004
n	55	26	
Week 3	0.7 (0.2)	1.5 (0.2)	0.004
n	56	28	
Month 1	0.3 (0.1)	0.6 (0.1)	0.110
n	58	30	
Month 2	0.2 (0.1)	0.5 (0.1)	0.081
n	56	29	

\* The mean and SEM (standard error of mean) were estimated from the ANOVA model that includes treatment, center and treatment by center interaction factors. P values for the test of treatment effect between two treatment groups were based on Type III analysis from the model described above.

Table 5. Patients with No Anterior Chamber Cell and Flare by Visit: No. (%) of Patients with No Anterior Chamber Cell and Flare

	Treatment Group		P*
	Active 1 and 2 DEX DDSs (n = 60)	Control Placebo DDS and No Treatment (n = 30)	
Day 3	2/58 (3)	1/29 (3)	1.000
Week 1	12/56 (21)	1/30 (3)	0.026
Week 2	23/55 (42)	5/26 (19)	0.046
Week 3	31/56 (55)	4/28 (14)	<0.001
Month 1	41/58 (71)	19/30 (63)	0.480
Month 2	46/56 (82)	19/29 (66)	0.087

\* P values for the test of treatment effect between two combined treatment groups were based on the Z test for difference in proportions between two groups.

compared to baseline ( $P = 0.009$  and  $P = 0.001$ , respectively). Mean IOPs remained below baseline levels in both groups through the remainder of the study.

Adverse events in the treated eye were seen in similar frequencies in the DEX DDS and control patients. Adverse events generally included symptoms related to the cataract surgery, such as posterior capsule opacity and eye discomfort.

## Discussion

Although steroids are widely used in the treatment of postoperative inflammation after cataract surgery, there are few studies in the literature documenting the efficacy of this treatment. When this study was initiated, rimexolone (Vexol, Alcon) was the only steroid that had been proved efficacious over placebo by a randomized, prospective study and approved by the United States Food and Drug Administration for the treatment of postoperative inflammation.<sup>9,10</sup> For this reason, the DEX DDS was compared to inactive controls (a placebo DDS and untreated patients) to clearly show the efficacy of this system in suppressing postoperative inflammation. Dexamethasone is a corticosteroid that suppresses the inflammatory response to a variety of agents.<sup>11</sup> For the purpose of suppressing inflammation, topical application of corticosteroids can achieve a high therapeutic level in the conjunctiva and cornea. However, intraocular absorption of a topical preparation is low. In rabbit eyes, only 1.1% of 80  $\mu\text{l}$  of topically applied, radioactively labeled dexamethasone reached the AC after 15 minutes.<sup>8</sup> More than 90% of a topically applied ocular drug may be absorbed systemically by the nasal and gastric mucosa.<sup>12</sup> In addition, intraocular drug concentration fluctuates between applications with peak concentration reached approximately 1 hour after application.<sup>13</sup>

Animal studies suggest that the 60  $\mu\text{g}$  of dexamethasone is released by the intraocular DEX DDS over a period of approximately 7 to 10 days (Oculex Pharmaceuticals, unpublished data). In two *in vivo* rabbit studies with the DEX DDS, dexamethasone in the AC reached a mean peak concentration of 0.63 to 2.1  $\mu\text{g}/\text{ml}$  on day 1 and a mean concentration of 0.10 to 0.36  $\mu\text{g}/\text{ml}$  on day 3 through day 9. Mean concentrations on day 11 were below 0.05  $\mu\text{g}/\text{ml}$ . In comparison, when two drops of 0.1% dexamethasone sodium phosphate (50  $\mu\text{l}$ ) were applied to the rabbit eye, dexamethasone phosphate in the aqueous humor reached a maximum concentration of 0.5  $\mu\text{g}/\text{ml}$  at 2 hours after instillation (mean = 0.19  $\mu\text{g}/\text{ml}$ ), quickly decreasing to a mean concentration of 0.04  $\mu\text{g}/\text{ml}$  by 3 hours (Oculex Pharmaceuticals, unpublished data).

A study in humans found that the peak concentration of dexamethasone alcohol in the aqueous humor was 31.0 ng/ml (0.031  $\mu\text{g}/\text{ml}$ )  $\frac{1}{2}$  to 2 hours after topical administration of 50  $\mu\text{l}$ . Mean concentrations decreased after this timepoint to a low of 3.1 ng/ml (0.003  $\mu\text{g}/\text{ml}$ ) at 8 to 13 hours.<sup>14</sup> Because the DEX DDS is placed in the posterior chamber, the amount of drug needed to achieve a therapeutic level is small compared to eyedrops, and systemic effects are unlikely.

Treatment with the DEX DDS was highly effective in early reduction and elimination of postoperative inflam-

mation in this trial. The statistically significant improvement in mean combined AC cell and flare scores in the DEX DDS-treated group versus the control group began at day 3 and persisted through week 3. This difference was seen even though more than 80% of the control patients had received concomitant topical anti-inflammatory medications by week 3.

After postoperative week 2, the mean AC cell and flare scores continued to be as low in the DEX DDS-treated patients as in the control patients, most of whom were taking topical anti-inflammatory medication. This suggests that rebound inflammation was not a frequent consequence of the relatively brief duration of drug delivery by the DEX DDS (7–10 days).

The majority (93%, 55 of 59) of DEX DDS-treated patients did not require any other anti-inflammatory therapy by the week-2 postoperative visit. An additional 5% (3 of 59) of DEX DDS-treated patients started taking a topical steroid or nonsteroidal anti-inflammatory drug at the third or fourth postoperative week. Because an insignificant intraocular level of dexamethasone would have been expected by this time, these few patients may have required more prolonged therapy for either persistent or rebound inflammation.

The effectiveness of the DEX DDS may be explained by rabbit studies, which show that the intraocular DEX DDS is able to achieve a higher level of aqueous dexamethasone than is possible with topical administration. In contrast to a rapidly declining drug level within 3 hours after eyedrop instillation, a prolonged, continuous dexamethasone level is maintained by the DEX DDS in rabbits.

Although this study was not designed to provide a direct comparison of intraocular DEX DDS versus topical dexamethasone delivery, a separate randomized, double-masked study conducted in Singapore has compared the DEX DDS with topical dexamethasone 0.1% for anti-inflammatory efficacy after cataract surgery.<sup>15</sup> In this study of 60 patients, AC flare, as measured with the Kowa FC500 Laser Flare Meter (Kowa Co. Ltd., Tokyo, Japan), was lower in the DEX DDS group than in the topical steroid group at all postoperative visits. The difference was statistically significant from postoperative day 4 through day 30 (all  $P$  values < 0.05). Mean slit-lamp AC cell and flare scores were also lower in the DEX DDS group at all postoperative visits, but the differences did not reach statistical significance. Additional larger studies comparing these two different delivery methods will be necessary to determine whether one treatment alternative is more efficacious than the other.

The DEX DDS appears to be well tolerated. The most frequent adverse events were those commonly associated with cataract surgery, and no difference in frequency was seen between the DEX DDS and control groups. The transient increase in IOP seen in all treatment groups at day 1 was probably attributable to the use of viscoelastic during surgery.<sup>16</sup> The outcome of implanting this product in steroid responders has not yet been determined. Of particular interest would be the extent to which the short duration of drug administration might abate this potential problem.

Whether used to administer antibiotic or anti-inflammatory medications, an ideal perioperative drug delivery sys-

tem for cataract surgery would have certain attributes. It would demonstrate superior efficacy by providing an adequately high and prolonged drug level at the desired site. It would be safe and would confine the drug action to the desired intraocular location, thereby avoiding systemic effect. It would be compatible with topical anesthesia and immediate vision. It would be short-acting enough to diminish the risks from side effects or allergy, but long-acting enough to obviate the necessity for postoperative topical therapy. Eliminating the need for patient self-medication would avoid problems with compliance and instruction. Further studies are warranted to confirm that the DEX DDS is able to provide some or all of these benefits.

The concept of a biodegradable intraocular drug delivery system can be extended to many other drugs and potential ocular applications as well. A desirable companion product for intraocular surgery would be an antibiotic DDS for endophthalmitis prophylaxis. Such products could be especially important in third-world settings where topical medications might not otherwise be available after intraocular surgery.

In conclusion, this multicenter, prospective, randomized, double-masked phase-II study has shown both the efficacy and safety of the DEX DDS in the treatment of inflammation after uncomplicated cataract surgery. Although the comparative efficacy of the DEX DDS versus conventional topical steroid was not addressed by this study, this product did show the potential to substitute for topical steroids in the majority of patients undergoing uncomplicated cataract surgery. Decreasing or eliminating the need for postoperative anti-inflammatory drops would be a significant benefit to most patients and would reduce physician time otherwise spent on instructing and monitoring patients receiving topical therapy.

## References

1. Leopold IH. Nonsteroidal and steroidal anti-inflammatory agents. In: Sears ML, Tarkkanen A, eds. *Surgical Pharmacology of the Eye*. New York: Raven Press, 1985;83-133.
2. Tennant JL. Cystoid maculopathy: prostaglandins in ophthalmology. In: Emery JM, ed. *Current Concepts in Cataract Surgery*. St. Louis: C.V. Mosby 1978;360-2.
3. Apple DJ, Solomon KD, Tetz MR, et al. Posterior capsule opacification. *Surv Ophthalmol* 1992;37:73-116.
4. Sanders DR, Kraff M. Steroidal and nonsteroidal anti-inflammatory agents. Effect on postsurgical inflammation and blood-aqueous humor barrier breakdown. *Arch Ophthalmol* 1984;102:1453-6.
5. Ferguson VMG, Spalton DJ. Recovery of the blood-aqueous barrier after cataract surgery. *Br J Ophthalmol* 1991;75:106-10.
6. Kass MA, Meltzer DW, Gordon M, et al. Compliance with topical pilocarpine treatment. *Am J Ophthalmol* 1986;101:515-23.
7. Winfield AJ, Jessiman D, Williams A, Esakowitz L. A study of the causes of non-compliance by patients prescribed eye-drops. *Br J Ophthalmol* 1990;74:477-80.
8. Ichigashira N, Yamaga N. Intraocular fate of dexamethasone disodium phosphate topically applied to the eyes of rabbits. *Steroids* 1978;32:615-28.
9. Assil KK, Massry G, Lehmann R, et al. Control of ocular inflammation after cataract extraction with rimexolone 1% ophthalmic suspension. *J Cataract Refract Surg* 1997;23:750-7.
10. Bron A, Denis P, Hoang Xuan TC, et al. The effects of Rimexolone 1% in postoperative inflammation after cataract extraction. A double-masked placebo-controlled study. *Eur J Ophthalmol* 1998;8:16-21.
11. Dexamethasone. Reynolds JEF, ed. *Martindale: the extra pharmacopoeia*, 31st ed. London: Pharmaceutical Press, 1996; 887-9.
12. Bodor N. Designing safer ophthalmic drugs. In: van der Goot H, Domany G, Pallos L, Timmerman H, eds. *Trends in Medicinal Chemistry '88*. Amsterdam: Elsevier Science Publishers, 1989;145-64.
13. Krupin T, Waltman SR, Becker B. Ocular penetration in rabbits of topically applied dexamethasone. *Arch Ophthalmol* 1974;92:312-4.
14. Watson D, Noble MJ, Dutton GN, et al. Penetration of topically applied dexamethasone alcohol into human aqueous humor. *Arch Ophthalmol* 1988;106:686-7.
15. Tan DTH, Chee S-P, Lim L, Lim ASM. Randomized clinical trial of a new dexamethasone delivery system (Surodex<sup>TM</sup>) for treatment of post-cataract surgery inflammation. *Ophthalmology* 1999;106:223-31.
16. Dada VK, Sindhu N, Sachdev MS. Postoperative intraocular pressure changes with use of different viscoelastics. *Ophthalmic Surg* 1994;25:540-4.