

# EFFECT OF AN INTRAVITREAL DEXAMETHASONE IMPLANT ON DIABETIC MACULAR EDEMA AFTER CATARACT SURGERY

PILAR CALVO, MD, PhD,\*† ANTONIO FERRERAS, MD, PhD,\*† FADWA AL ADEL, MD, FRCSC,‡  
WANTANEE DANGBOON, MD,§ MICHAEL H. BRENT, MD, FRCSC¶

**Purpose:** To analyze the effects of a dexamethasone intravitreal implant (DEX; Ozurdex 700  $\mu\text{g}$ ; Allergan) administered immediately after cataract surgery in diabetic patients.

**Methods:** This prospective, single-arm, open label study (NCT01748487 at ClinicalTrials.gov) involved Type 2 diabetic patients with at least mild diabetic retinopathy (DR) who underwent cataract surgery and DEX insertion after phacoemulsification, and intraocular lens implantation were enrolled. Best-corrected visual acuity and central retinal thickness (CRT) measured by spectral-domain optical coherence tomography were recorded at 1 week preoperatively, and 1 week, 1 month, and 3 months after surgery. Adverse events were also recorded.

**Results:** Twenty-four eyes of 24 patients (17 [70.8%] men; mean age  $63.7 \pm 8.7$  years) with mild nonproliferative DR (41.7%), moderate nonproliferative DR (33.3%), severe nonproliferative DR (16.7%), or treated proliferative DR (8.3%) were selected. After DEX treatment, mean CRT changed from  $241.1 \mu\text{m}$  (95% confidence interval,  $227.5\text{--}254.6 \mu\text{m}$ ) at baseline to  $236.9 \mu\text{m}$  (95% confidence interval,  $223.9\text{--}249.9 \mu\text{m}$ ) at 1 week ( $P = 0.09$ ),  $238.9 \mu\text{m}$  (95% confidence interval,  $225.5\text{--}252.3 \mu\text{m}$ ) at 1 month ( $P = 0.44$ ), and  $248 \mu\text{m}$  (95% confidence interval,  $232.4\text{--}260.8 \mu\text{m}$ ) at 3 months ( $P = 0.15$ ). No eyes showed a postoperative increase  $>50 \mu\text{m}$  in the CRT at any visit. A 10% increase in CRT was found in 8.3% of eyes. Mean best-corrected visual acuity significantly improved from 0.37 (20/50) at baseline to 0.19 (20/30) at 1 week, 0.12 (20/25) at 1 month, and 0.12 (20/25) at 3 months ( $P < 0.001$  for each comparison). Mean intraocular pressure before surgery was 13.8 mmHg, and none of the patients developed an intraocular pressure  $\geq 22$  mmHg at any visit. None of the patients developed any serious adverse events during the follow-up.

**Conclusion:** These short-term results suggest that a single DEX injection intraoperatively after phacoemulsification could avoid an increase in CRT after cataract surgery in diabetic patients.

RETINA 38:490–496, 2018

Diabetes mellitus is estimated to affect 387 million people worldwide and its prevalence is increasing as a pandemic chronic disease that may affect as many as 700 million people by the year 2035.<sup>1</sup> Macular edema (ME) is a serious complication for the diabetic population,<sup>2</sup> which if left untreated can lead to irreversible severe vision loss.<sup>3,4</sup> Cataracts are another major cause of vision loss in patients with diabetes mellitus, and patients with diabetes mellitus are also more likely than nondiabetic patients to develop cataracts because of the inherent metabolic condition of the disease.<sup>5,6</sup> Therefore, a large percentage of diabetic

patients undergo cataract surgery every year, and  $\sim 22\%$  of them develop ME.<sup>7</sup> Patients with preexisting diabetic retinopathy (DR) seem to be at even greater risk of DR progression and diabetic ME after cataract surgery. Therefore, the development of better approaches to address and treat ME, or even to prevent ME, is crucial.<sup>7</sup>

Numerous therapies are used to treat pseudophakic ME. Triamcinolone acetonide (TA) injections are used off-label to treat ME,<sup>8–10</sup> but as TA is white and opaque, it can potentially impair vision by migrating into the macula. Furthermore, intravitreal TA is often associated

with an increase in intraocular pressure (IOP) by as much as 40% from preintraocular TA levels,<sup>11</sup> which limits its use and makes TA an unacceptable treatment option for patients with concomitant glaucoma. Less frequently used, anti-vascular endothelial growth factor agents like ranibizumab,<sup>12,13</sup> bevacizumab,<sup>14,15</sup> and pegaptanib<sup>16</sup> are also off-label agents to treat pseudophakic ME. These drugs are effective in preventing or decreasing the usual postoperative increase in central retinal thickness (CRT) in diabetic patients, but they are expensive, have potential adverse vascular effects,<sup>17,18</sup> and may also impair wound healing.<sup>19</sup>

Based on the results of the MEAD study,<sup>20</sup> the US Food and Drug Administration recently approved the use of a sustained-release biodegradable 700  $\mu$ g dexamethasone intravitreal implant (DEX; Ozurdex; Allergan Inc, Irvine, CA) for treating diabetic macular edema (DME), especially for pseudophakic eyes or patients undergoing cataract surgery. This drug delivery system is well tolerated,<sup>21</sup> and results in improvements in visual acuity, macular thickness, and fluorescein leakage in patients with persistent ME.

The purpose of the present study was to assess the feasibility and clinical effectiveness of DEX administered immediately after cataract surgery in diabetic patients to prevent the occurrence of ME.

## Methods

This prospective, single-arm, open label study (registered with the identifier NCT01748487 at ClinicalTrials.gov) involved Type 2 diabetic patients

---

From the \*IIS-Aragon, Ophthalmology Department, Miguel Servet University Hospital, Zaragoza, Spain; †University of Zaragoza, Zaragoza, Spain; ‡Department of Ophthalmology, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia; §Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand; and ¶Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada.

Supported in part by Allergan plc, Dublin, Ireland. The funding organization had no role in the design or conduct of this research.

P. Calvo (Lecture fees: Novartis Ophthalmics, Thea; Travel fees: Novartis Ophthalmics, Bayer Healthcare, Alcon Laboratories, Allergan); A. Ferreras (Board Membership: Carl Zeiss Meditec; Lecture fees: Carl Zeiss Meditec; Research support: Oculus, Carl Zeiss Meditec; Travel fees: Novartis Ophthalmics, Bayer Healthcare, Alcon Laboratories, Allergan); M. H. Brent (Board Membership: Novartis Ophthalmics, Bayer Healthcare, Alcon Laboratories; Research support: Novartis Ophthalmics, Allergan). The remaining authors have no financial/conflicting interests to disclose.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Reprint requests: Michael H. Brent, MD, FRCSC, Toronto Western Hospital, 399 Bathurst Street, 6th Floor, New East Wing, Room 423, Toronto, ON M5T 2S8, Canada; e-mail: mh.brent@utoronto.ca

with at least mild DR who underwent cataract surgery and DEX administered immediately after phacoemulsification and intraocular lens (IOL) implantation. The design of the study followed the tenets of the Declaration of Helsinki and the protocol was approved by Health Canada and the Institutional Research Ethics Board at the University Health Network, Toronto, Canada. Diabetic patients referred for cataract surgery who met the inclusion criteria and provided written informed consent to the Ophthalmology Department of the Toronto Western Hospital between June 2013 and June 2015 were consecutively and prospectively enrolled into the study. Twenty-four adult Type 2 diabetic patients with lens opacity (nuclear color and opalescence, cortical or posterior subcapsular lens opacity >3) according to the Lens Opacities Classification System III system<sup>22</sup>; and DR of at least Level 20 (microaneurysms only) as defined by the Early Treatment Diabetic Retinopathy Study were recruited for the study.<sup>23</sup> Patients had to be healthy enough to undergo cataract surgery as determined by their physicians.

Exclusion criteria included a history of ocular surgery, inflammation, active or suspected ocular or periocular infections, advanced glaucoma (baseline IOP higher than 21 mmHg or use of more than one type of glaucoma medication), history of steroid-induced IOP increase, panretinal photocoagulation within 3 months of study entry, and retinal or choroidal disease other than DR that could affect CRT. Patients with cataract precluding proper optical coherence tomography (OCT) measurement and those with significant DME measured by OCT preoperatively (CRT > 300  $\mu$ m) were excluded. Eyes that developed intraoperative complications leading to aphakia, AC IOL or a posterior capsular rupture were excluded. Diabetic patients without any DR and those with active iris or retinal neovascularization before cataract surgery were also excluded. If a patient required bilateral cataract extraction, only one eye was included in the study.

## Intervention

All patients underwent cataract extraction by a single surgeon (MHB) under topical anesthesia through a 2.7-mm temporal clear corneal incision, continuous curvilinear capsulorhexis, and standard phacoemulsification. The IOL was implanted in the capsular bag. Before removing the eye speculum, DEX was administered at the end of the procedure. An applicator system was used to insert the DEX implant into the vitreous through a pars plana puncture as described previously.<sup>24</sup> All patients had the same medication regimen: application of fourth-generation fluoroquinolone (gatifloxacin) drops was prescribed four times a day as part of the

patient's postoperative medication for 1 week after surgery. A topical nonsteroidal antiinflammatory drug (NSAID, nepafenac, Nevanac, Alcon Research Ltd, Fort Worth, TX) was used three times a day for 3 weeks after surgery and a topical steroid (dexamethasone 0.1% suspension) was used four times a day after surgery and slowly tapered over 4 weeks.

Patients were seen 1 week preoperatively (baseline visit), and on the same day after surgery (Visit 1), at 1 week (Visit 2), 1 month (Visit 3), and 3 months (Visit 4) after surgery. Patient characteristics, such as age, sex, duration of the diabetes, hemoglobin A1c, medication use (i.e., acetylcholinesterase inhibitor or beta-blockers), and type of diabetes, were recorded at the baseline visit. All patients underwent a complete ophthalmologic examination. Efficacy evaluations included best-corrected visual acuity (BCVA) using logarithmic size progression (logMAR charts), Cirrus HD-OCT (software version 5.0 or higher; Carl Zeiss Meditec Inc, Dublin, CA), slit-lamp biomicroscopy, IOP measured by the Goldman applanation tonometer, and dilated fundus exam. Diabetic retinopathy was classified in accordance with the Early Treatment Diabetic Retinopathy Study guidelines.<sup>23</sup>

The primary outcome measure was the mean change in CRT from baseline to 3 months as measured by OCT. Secondary outcome measures included mean change in BCVA from baseline to the end of the study, macular volume, development of ME, and incidence of any additional treatment (e.g., focal laser, anti-vascular endothelial growth factor injections) at each study visit. Any ocular or systemic adverse events were recorded and treated accordingly.

Central retinal thickness and macular volume were measured using the Cirrus HD-OCT. The protocol used was the 512 × 128 scan pattern where a 6 mm × 6 mm area on the retina was scanned with 128 horizontal lines, each comprising 512 A-scans per line (total of 65,536 sampled points) within a scan time of 2.4 seconds. Each study eye was previously pharmacologically dilated with 2.5% phenylephrine hydrochloride. A senior technician obtained all scans. Only good-quality examinations with a signal strength of 6/10 or better were retained. Optical coherence tomography data were processed using the software mentioned above. Intrinsic retinal segmentation algorithms were used to define an internal and an external retinal layer position from which retinal thickness and volume measurements were derived. In the computational software, retinal thicknesses are averaged within nine retinal subfields in a 6-mm diameter circle centered on the fovea, known as Early Treatment Diabetic Retinopathy Study Grid. The central circle has a radius of 500 μm (1 mm diameter). Overall macular volume (cube volume, cubic

millimeter) and the cube mean thickness (micrometer) over the entire grid area were also obtained from the computational software.

### Statistics

Data were analyzed using IBM SPSS Statistics (version 19 or higher) and MedCalc software, with the level of statistical significance set at  $P < 0.05$ . The minimum sample size was 24 eyes, considering a difference of  $50 \pm 10 \mu\text{m}$  for the CRT as significant, with a Type 1 error rate of 0.01, and a power (Type 2 error) of 90% (analysis performed with MedCalc software version 11.4.1.0; MedCalc software, Mariakerke, Belgium). Descriptive statistics were used to describe characteristics of the sample (e.g., sex, age, cataract severity, and diabetes duration) using measures of central tendency and dispersion (e.g., mean values, medians, ranges, standard deviation, and 95% confidence intervals (CIs), or proportions where appropriate). The mean values for BCVA, IOP, CRT, and macular volume at baseline and at each follow-up visit were compared using the one-sample *t*-test.

## Results

### Study Population

Twenty-four eyes of 24 patients (17 [70.8%] men, mean age  $63.7 \pm 8.7$  years) were selected. The clinical characteristics of the diabetic patients are summarized in Table 1. The right eye was the study eye in 62.5% of the cases. High blood pressure was detected in 79.2% of the patients. Regarding the level of DR, 41.7% of the patients had mild nonproliferative DR (NPDR); 33.3% had moderate NPDR, 16.7% had severe NPDR, and 8.3% had treated proliferative DR. None of the patients had been treated previously for DME. Main clinical outcomes of DEX in diabetic patients after cataract surgery at different time points are summarized in Table 2.

### Anatomic Changes

To evaluate postoperative changes in CRT, we measured it before and at 1 week, 1 month, and 3 months after cataract surgery. After DEX treatment, the mean CRT changed from 241.1 μm (95% CI, 227.5–254.6 μm) at baseline to 236.9 μm (95% CI, 223.9–249.9 μm) at 1 week ( $P = 0.09$ ), 238.9 μm (95% CI, 225.5–252.3 μm) at 1 month ( $P = 0.44$ ), and 248 μm (95% CI, 232.4–260.8 μm) at 3 months ( $P = 0.15$ ). Mean macular volume (cubic millimeter) was 9.72 at baseline and did not change significantly at

Table 1. Baseline Clinical Characteristics of Diabetic Patients

	Mean ± SD
Age, years	63.7 ± 8.7
DM duration, years	19 ± 9.5
LogMAR BCVA (Snellen)	0.37 ± 0.21 (20/50)
IOP, mmHg	13.8 ± 3.1
CRT, $\mu\text{m}$	241.1 ± 32.1
Macular volume, $\text{mm}^3$	9.72 ± 0.66
N	24

DM, diabetes mellitus; BCVA, best corrected visual acuity; IOP, intraocular pressure; CRT, central retinal thickness; N, number of subjects.

1 week (9.70,  $P = 0.66$ ), 1 month (9.72,  $P = 0.77$ ), or 3 months (9.81,  $P = 0.53$ ).

The relationship of CRT before surgery to that at 1 week, 1 month, and 3 months after DXI was examined to gain an outlook into the thickness changes. No eyes showed a postoperative increase  $>50 \mu\text{m}$  in the CRT at any visit (Figure 1, A–C). A 10% increase in CRT was found in 8.3% of eyes. None of the eyes developed central-involved ME on OCT imaging or clinically significant ME.

#### Changes in Best-Corrected Visual Acuity

Mean BCVA significantly improved from 0.37 (20/50) at baseline to 0.19 (20/30) at 1 week, 0.12 (20/25) at 1 month, and 0.12 (20/25) at 3 months ( $P < 0.001$  for all comparisons). None of the patients had a reduction in their vision, and 50% of them achieved greater than 0.2 logMAR units (10 letters) or more improvement in BCVA, with 31% of them achieving  $>0.3$  logMAR units (15 letters) of improvement. Figure 2 shows the changes in BCVA between before and at month 3 after surgery.

#### Safety

Regarding additional treatment during the study, 87.5% of the cases (22/24) required no additional treatment. Two patients required additional topical

steroid treatment (prednisone acetate drops) because of anterior segment inflammation.

Assessment by clinical examination revealed no change in the DR severity from baseline in 22 eyes (91.6%). One patient improved one step from severe NPDR to moderate NPDR, and another patient worsened one step from mild NPDR to moderate NPDR.

Mean IOP before surgery was 13.8 mmHg. There was no significant increase of IOP at 1 week (14.5 mmHg;  $P = 0.33$ ), 1 month (14.4 mmHg;  $P = 0.36$ ), or 3 months (13.3 mmHg;  $P = 0.23$ ). None of the patients developed an IOP greater than 22 mmHg, and none of them required any IOP-lowering medications at any time during the study.

All patients had uncomplicated cataract surgery and DEX injection. No patients suffered severe ocular (e.g., endophthalmitis, retinal detachment) or systemic adverse effects during the follow-up period.

## Discussion

To the best of our knowledge, this study is the first showing that a single DEX injection intraoperatively after cataract phacoemulsification could prevent an increase in macular thickness after cataract surgery in diabetic patients with at least mild DR and without ME at the time of the surgery. In this study, the anatomic stability based on clinical exam, CRT and macular volume measurements, and the clinically meaningful improvement in BCVA were sustained for 3 months after treatment.

Agarwal et al<sup>25</sup> injected DEX in eight diabetic patients before phacoemulsification and observed a significant gain in visual acuity ( $P < 0.001$ ) at 6, 12, and 24 weeks in this group compared with the control group. They also reported a significant increase ( $P < 0.03$ ) in CRT at every visit in the control group compared with the DEX group. They found no difference in the IOP values between the two groups. In contrast to our study, they performed the study DEX injection at the beginning of the cataract surgery. Special caution is advised in aphakic patients, patients with AC

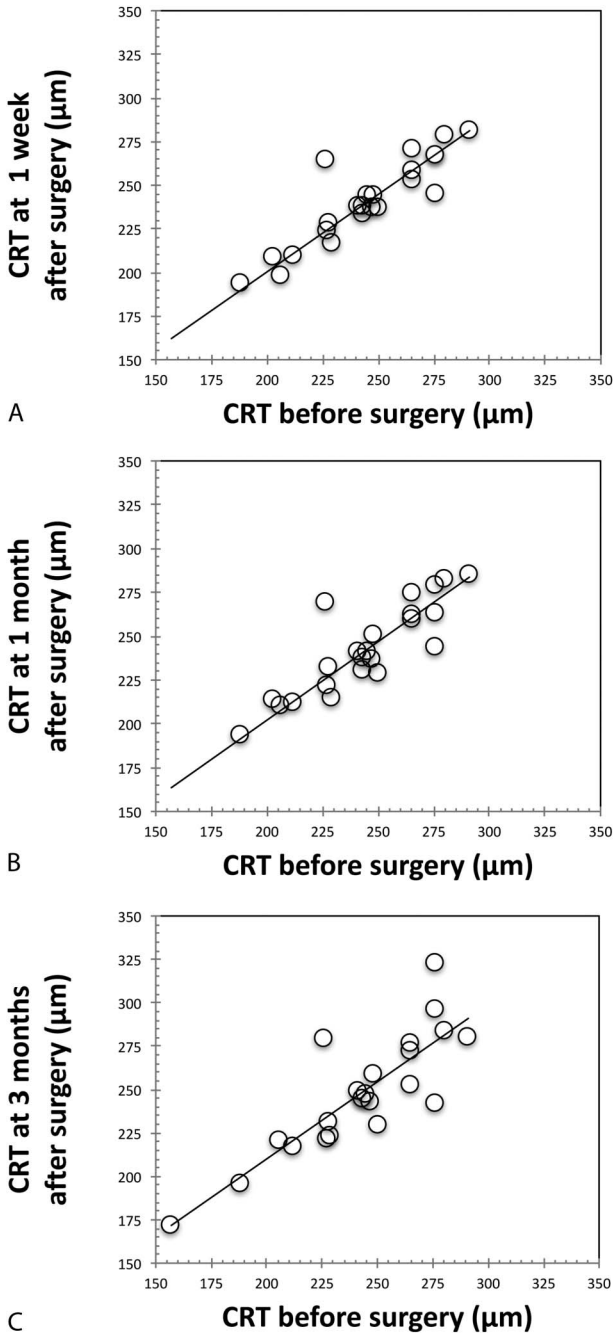
Table 2. Clinical Outcomes of Intravitreal Dexamethasone Implant in Diabetic Patients After Cataract Surgery at Different Time Points

	Baseline	1 Week	1 Month	3 Months	$P^*$
BCVA LogMAR (Snellen)	0.37 (20/50)	0.19 (20/30)	0.12 (20/25)	0.12 (20/25)	<b><math>&lt;0.001</math></b>
IOP, mmHg	13.8	14.5	14.4	13.3	$>0.05$
CRT (95% CI), $\mu\text{m}$	241.1 (227.5–254.6)	236.9 (223.9–249.9)	238.9 (225.5–252.3)	248 (232.4–260.8)	$>0.05$
Macular volume, $\text{mm}^3$	9.72	9.70	9.72	9.96	$>0.05$

$P$ -value represents the comparison across each visit (1 week, 1 month, and 3 months).

Significant differences ( $P < 0.05$ ) are highlighted in bold front.

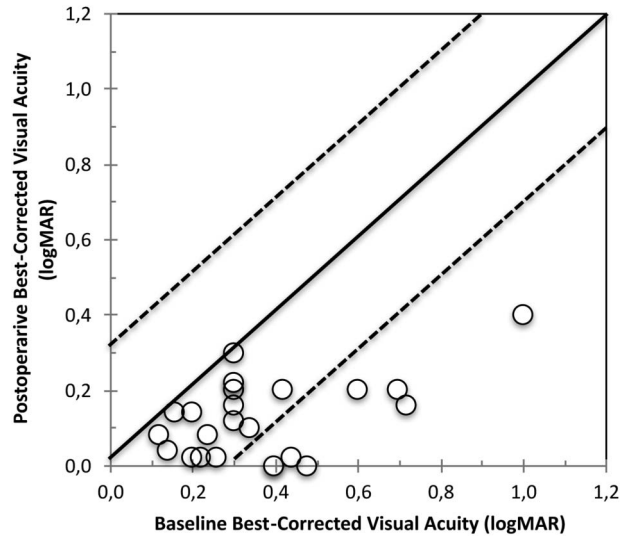
\*One-sample Student's  $t$ -test.



**Fig. 1.** Central retinal thickness of diabetic patients measured at baseline versus 1 week (A), 1 month (B), and 3 months (C) after cataract surgery.

IOL, posterior capsular rupture, or previous pars plana vitrectomy because of the risk of migration of the DEX into the AC, which may result in corneal edema and corneal endothelial damage.<sup>26</sup> In this study, DEX was injected at the end of the procedure, after the cataract was safely removed and the IOL correctly placed in the capsular bag.

Sze et al<sup>27</sup> published a retrospective case series, including 12 DME patients and 12 patients with ME



**Fig. 2.** Scatter plot of baseline BCVA versus BCVA at 3 months after cataract surgery. All points below the solid line imply improved final BCVA. Two broken lines above and below the solid line demarcate a stripe within which the difference of BCVA was <3 lines. logMAR, logarithm of the minimum angle of resolution.

secondary to retinal vein occlusion. All of them presented significant vision loss and ME before surgery (mean VA was 20/200, and CRT was  $530.2 \pm 218.9 \mu\text{m}$ ) and underwent phacoemulsification and DEX at the same time. They found a significant improvement in vision to 20/66 ( $P = 0.003$ ) and significant decrease in CRT to  $300.7 \pm 78.1 \mu\text{m}$  ( $P < 0.001$ ). There was no significant change in IOP ( $P > 0.05$ ).

The distinction between DME and Irvine–Gass syndrome (pseudophakic ME) in these cases is challenging, as the preexisting disease (DME) is a known risk factor for ME after surgery. Khurana et al<sup>28</sup> reported the prospective results of DEX in 7 diabetic patients who developed pseudophakic ME within 4 weeks to 10 weeks after uncomplicated cataract surgery despite ongoing prophylactic treatment with NSAID and steroid eye drops. Clinically significant improvements in vision accompanied by reductions in CRT and macular volume were sustained up to 6 months posttreatment. They did not find a significant change in mean IOP at any time during the study.

Notably, with the projected increasing prevalence of diabetes mellitus,<sup>1</sup> the number of diabetic patients with cataracts is also expected to increase over the next several years. The incidence of clinical ME after small-incision phacoemulsification ranges between 0.1% and 2.35%, but in diabetic patients with a history of DME treatment may be as high as 20%.<sup>29–31</sup> The natural course of ME in diabetic patients after cataract surgery remains controversial. The large disparity in the incidence of this worsening can be explained, at least in part, to the different methodology used to

study postoperative increase of ME (depending on whether the diagnosis was confirmed by OCT, fluorescein angiography, or clinical examination alone). The pathophysiology of pseudophakic CME remains unclear. The principal cause seems to be inflammatory mediators that break down the blood retinal barrier, leading to increased vascular permeability, pericytes, and endothelial cell loss.<sup>32</sup>

The inflammatory signal process after cataract surgery is believed to be short-lived, as ME may develop in as little as 1 month after surgery. Even in routine cataract surgery, ME can develop secondary to the inflammatory cascade, despite the use of postoperative steroid eye drops.<sup>33</sup> We believe that injecting DEX directly into the eye where it is needed at the beginning of this inflammatory signal cascade could blunt or prevent the occurrence of ME among diabetics, as demonstrated by this study.

Intravitreal injections effectively deliver an adequate drug concentration for treating posterior eye disease. The short half-life (<4 hours) of dexamethasone after a single intravitreal injection into the vitreous humor, however, was an important limitation<sup>34</sup> until the advent of an intravitreal biodegradable drug delivery system (Novadur; Allergan Inc), which allows for the controlled release of dexamethasone after it has been injected into the eye through a 23-gauge pars plana puncture. DEX is a free-floating biodegradable copolymer, polylactic-co-glycolic acid containing micronized dexamethasone. The copolymer gradually undergoes hydrolysis to carbon dioxide and water, whereas dexamethasone is slowly distributed into vitreous cavity.<sup>21</sup> In monkey eyes, the peak concentration of DEX was achieved during the first 2 months, followed by a low release rate up to 6 months.<sup>35,36</sup>

The most frequent ocular side effect is steroid-induced glaucoma. Generally, the increase in IOP is transitory, and the IOP returns to pretreatment levels within 1 week to 3 weeks after stopping dexamethasone.<sup>37,38</sup> Thus far, none of the 24 patients have experienced a significant increase in IOP after DEX. However, about 30% of patients using DEX will suffer a significant increase in IOP, requiring medical treatment. The use of DEX in patients with advanced glaucoma or those using maximum topical medication must be carefully evaluated because of their higher risk of uncontrolled IOP rise. The time to peak IOP is approximately 60 days after implantation, returning to baseline within 6 months. Most patients are successfully controlled with topical IOP-lowering medication. Less than 1% to 2% of the eyes receiving DEX require a surgical procedure to reduce IOP.<sup>20,21</sup> The response to DEX usually lasts between 3 months and 6 months, so more time may be needed to determine whether

changes in the IOP will occur if repeated injections are required.

The strengths of this study include the prospective design, the use of spectral-domain optical coherence tomography, and the standardized Early Treatment Diabetic Retinopathy Study protocol. The main limitations were the relatively small sample size and the lack of a control arm.

In conclusion, excellent anatomic outcomes were obtained using a single DEX after cataract surgery in Type 2 diabetic patients. Taken together, the results of previous studies<sup>25,27,28</sup> and this study suggest that DEX may be a promising therapy for postsurgical ME in diabetic patients. However, the indiscriminate use of prophylactic DEX in all diabetic patients could result in some patients receiving an unnecessary treatment and may not be warranted. Despite disparities amongst studies in terms of protocol design, baseline characteristics and endpoints, a limited comparison for ME development after cataract surgery is possible by analyzing the number needed to treat based on the available data. The patient must be aware of all the risks and benefits using DEX before the final decision is taken. Further studies are needed to identify the diabetic patients at higher risk of developing ME and confirm the long-term outcomes and safety of DEX after uncomplicated cataract surgery.

**Key words:** diabetes, cataract, diabetic macular edema, optical coherence tomography, dexamethasone, intravitreal.

### Acknowledgments

The authors thank Olivera Karanovic, MD, CCRC II (Research Study Coordinator); Caitlin Falcon (Ophthalmic Assistant); and Joanne Thorne (Ophthalmic Assistant and Office Manager to Dr. Michael Brent) for their support.

### References

1. International Diabetes Federation. The IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.
2. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology* 1984;91:1464–1474.
3. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985;103:1796–1806.
4. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 2. Early Treatment Diabetic Retinopathy Study research group. *Ophthalmology* 1987;94:761–774.

5. Arnal E, Miranda M, Almansa I, et al. Lutein prevents cataract development and progression in diabetic rats. *Graefes Arch Clin Exp Ophthalmol* 2009;247:115–120.
6. Chan AW, Ho YS, Chung SK, Chung SS. Synergistic effect of osmotic and oxidative stress in slow-developing cataract formation. *Exp Eye Res* 2008;87:454–461.
7. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. *Ophthalmology* 2007;114:881–889.
8. Jonas JB, Kreissig I, Kampeter B, Degenring RF. Intravitreal triamcinolone acetonide for the treatment of intraocular edematous and neovascular diseases [in German]. *Ophthalmologie* 2004;101:113–120.
9. Ladjimi A, Zeghidi H, Ben Yahia S, et al. Intravitreal injection of triamcinolone acetonide for the treatment of macular edema [in French]. *J Fr Ophthalmol* 2005;28:749–757.
10. Sorensen TL, Haamann P, Villumsen J, Larsen M. Intravitreal triamcinolone for macular oedema: efficacy in relation to aetiology. *Acta Ophthalmol Scand* 2005;83:67–70.
11. Boscia F, Furino C, Dammacco R, et al. Intravitreal triamcinolone acetonide in refractory pseudophakic cystoid macular edema: functional and anatomic results. *Eur J Ophthalmol* 2005;15:89–95.
12. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064–1077.
13. Nguyen QD, Shah SM, Heier JS, et al. Primary end point (six months) results of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology* 2009;116:2175–2181.
14. 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;28:1053–1060.
15. Takamura Y, Kubo E, Akagi Y. Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery. *Ophthalmology* 2009;116:1151–1157.
16. Cervera E, Diaz-Llopis M, Udaondo P, Garcia-Delpech S. Intravitreal pegaptanib sodium for refractory pseudophakic macular oedema. *Eye (Lond)* 2008;22:1180–1182.
17. Jeganathan VS, Verma N. Safety and efficacy of intravitreal anti-VEGF injections for age-related macular degeneration. *Curr Opin Ophthalmol* 2009;20:223–225.
18. Simo R, Hernandez C. Intravitreal anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. *Diabetologia* 2008;51:1574–1580.
19. Tezel TH, Kaplan HJ. Are intravitreal anti-VEGF antibodies safe? *Ocul Immunol Inflamm* 2007;15:1–2.
20. Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014;121:1904–1914.
21. 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.
22. Chylack LT Jr, Wolfe JK, Singer DM, et al. The lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. *Arch Ophthalmol* 1993;111:831–836.
23. Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110:1677–1682.
24. Haller JA, Bandello F, Belfort R Jr, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134–1146.
25. Agarwal A, Gupta V, Ram J, Gupta A. Dexamethasone intravitreal implant during phacoemulsification. *Ophthalmology* 2013;120:211. e1–5.
26. Khurana RN, Appa SN, McCannel CA, et al. Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. *Ophthalmology* 2014;121:67–71.
27. Sze AM, Luk FO, Yip TP, et al. Use of intravitreal dexamethasone implant in patients with cataract and macular edema undergoing phacoemulsification. *Eur J Ophthalmol* 2015;25:168–172.
28. Khurana RN, Palmer JD, Porco TC, Wieland MR. Dexamethasone intravitreal implant for pseudophakic cystoid macular edema in patients with diabetes. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:56–61.
29. Baker CW, Almkhater T, Bressler NM, et al. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. *JAMA Ophthalmol* 2013;131:870–879.
30. Chu CJ, Johnston RL, Buscombe C, et al; United Kingdom Pseudophakic Macular Edema Study Group. Risk factors and incidence of macular edema after cataract surgery: a database study of 81984 eyes. *Ophthalmology* 2016;123:316–323.
31. Romero-Aroca P, Fernández-Ballart J, Almena-García M, et al. Nonproliferative diabetic retinopathy and macular edema progression after phacoemulsification: prospective study. *J Cataract Refract Surg* 2006;32:1438–1444.
32. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. *Curr Opin Ophthalmol* 2012;23:26–32.
33. Kim SJ, Jampel H. Prevention of cystoid macular edema after cataract surgery in non-diabetic and diabetic patients: a systematic review and meta-analysis. *Am J Ophthalmol* 2016;161:221–222.
34. Kwak HW, D'Amico DJ. Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection. *Arch Ophthalmol* 1992;110:259–266.
35. Chang-Lin JE, Attar M, Acheampong AA, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest Ophthalmol Vis Sci* 2011;52:80–86.
36. Chang-Lin JE, Burke JA, Peng Q, et al. Pharmacokinetics of a sustained-release dexamethasone intravitreal implant in vitrectomized and nonvitrectomized eyes. *Invest Ophthalmol Vis Sci* 2011;52:4605–4609.
37. Pleyer U, Ursell P, Rama P. Intraocular pressure effects of common topical steroids for post-cataract inflammation: are they all the same? *Ophthalmol Ther* 2013;2:55–72.
38. Chang DF, Tan JJ, Tripodis Y. Risk factors for steroid response among cataract patients. *J Cataract Refract Surg* 2011;37:675–681.