Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion

Twelve-Month Study Results

Julia A. Haller, MD,1 Francesco Bandello, MD,2 Rubens Belfort Jr, MD,3 Mark S. Blumenkranz, MD,4 Mark Gillies, MD,5 Jeffrey Heier, MD,6 Anat Loewenstein, MD,7 Young Hee Yoon, MD,8 Jenny Jiao, PhD,9 Xiao-Yan Li, MD,9 Scott M. Whitcup, MD,9 for the Ozurdex GENEVA Study Group*

Objective: To evaluate the safety and efficacy of 1 or 2 treatments with dexamethasone intravitreal implant (DEX implant) over 12 months in eyes with macular edema owing to branch or central retinal vein occlusion (BRVO or CRVO).

Design: Two identical, multicenter, prospective studies included a randomized, 6-month, double-masked, sham-controlled phase followed by a 6-month open-label extension.

Participants: We included 1256 patients with vision loss owing to macular edema associated with BRVO or CRVO.

Methods: At baseline, patients received DEX implant 0.7 mg (n = 421), DEX implant 0.35 mg (n = 412), or sham (n = 423) in the study eye. At day 180, patients could receive DEX implant 0.7 mg if best-corrected visual acuity (BCVA) was < 84 letters or retinal thickness was > 250 μm.

Main Outcome Measures: The primary outcome for the open-label extension was safety; BCVA was also evaluated.

Results: At day 180, 997 patients received open-label DEX implant. Except for cataract, the incidence of ocular adverse events was similar in patients who received their first or second DEX implant. Over 12 months, cataract progression occurred in 90 of 302 phakic eyes (29.8%) that received 2 DEX implant 0.7 mg injections versus 5 of 88 sham-treated phakic eyes (5.7%); cataract surgery was performed in 4 of 302 (1.3%) and 1 of 88 (1.1%) eyes, respectively. In the group receiving two 0.7-mg DEX implants (n = 341), a ≥10-mmHg intraocular pressure (IOP) increase from baseline was observed in (12.6% after the first treatment, and 15.4% after the second). The IOP increases were usually transient and controlled with medication or observation; an additional 10.3% of patients initiated IOP-lowering medications after the second treatment. A ≥15-letter improvement in BCVA from baseline was achieved by 30% and 32% of patients 60 days after the first and second DEX implant, respectively.

Conclusions: Among patients with macular edema owing to BRVO or CRVO, single and repeated treatment with DEX implant had a favorable safety profile over 12 months. In patients who qualified for and received 2 DEX implant injections, the efficacy and safety of the 2 implants were similar with the exception of cataract progression.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. Ophthalmology 2011;118:2453–2460 © 2011 by the American Academy of Ophthalmology.

*Group members listed online (available at http://aaojournal.org)

Macular edema is a common complication of both branch and central retinal vein occlusion (BRVO and CRVO). It can be persistent and difficult to treat; it is among the most prevalent causes of vision loss in both of these conditions.1

The results of recent randomized, controlled trials have shown that laser photocoagulation,2 intravitreal therapy with the antivascular endothelial growth factor agent ranibizumab,3,4 and the corticosteroids triamcinolone acetonide2,5 and dexamethasone,6,7 can be of benefit in the treatment of macular edema associated with BRVO or CRVO. These studies also show, however, that repeated treatments are often required to control macular edema, prevent vision loss, and increase the chance of visual improvement.

A sustained delivery, biodegradable dexamethasone intravitreal implant (DEX implant; Ozurdex; Allergan, Inc., Irvine, CA) has been shown in phase III, randomized, controlled trials to reduce macular edema and improve visual acuity in patients with BRVO and CRVO, with effects sustained for up to 6 months after a single injection.7 In these initial, 6-month studies, DEX implant treatment was...
well tolerated. The steroid-induced increases in intraocular pressure (IOP) that occurred in some patients were transient and typically successfully managed with observation or IOP-lowering medication, and cataract progression was uncommon. To further evaluate the safety of DEX implant, the studies were extended in an open-label manner at 6 months, with DEX implant 0.7 mg administered to all patients as needed at month 6 according to study-defined criteria. The present report describes the results of the 12-month safety and efficacy evaluations of single and repeated DEX implant treatments.

Methods

Study Design

Two identical, prospective, multicenter, phase III clinical trials were conducted. Each trial consisted of a 6-month, randomized, sham-controlled, parallel-group, double-masked phase followed by a 6-month open-label extension. Each of the trials enrolled both BRVO and CRVO patients. The protocol for the initial, 6-month, double-masked phase of the trials has been described in detail previously and is summarized later.

Both trials were conducted in compliance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Institutional review board/ethics committee approval was obtained at each investigational site, and informed consent was obtained from all patients. These trials are registered at clinicaltrials.gov as NCT00168324 and NCT00168298. The results of the 2 trials were pooled for analysis.

Patient Population

The primary patient eligibility criteria for the study are listed in Table 1 (available online at http://aaojournal.org). Enrolled patients were ≥18 years of age and had decreased visual acuity as a result of clinically detectable macular edema associated with CRVO or BRVO. Disease duration was required to be between 6 weeks and 9 months in eyes with CRVO and between 6 weeks and 12 months in eyes with BRVO before initiation of therapy. Best-corrected visual acuity (BCVA) was required to be between 34 (20/200) and 68 letters (20/50) in the study eye and >34 letters in the nonstudy eye. Retinal thickness in the central subfield (as measured by optical coherence tomography; OCT2 or OCT3) had to be ≥300 μm in the study eye. The investigators excluded eyes judged to have significant ischemia on fluorescein angiography or any other condition precluding likelihood of visual improvement.

Study Treatment

On study entry at baseline (day 0), study eyes were randomized to either a sham procedure or treatment with DEX implant 0.7 mg or 0.35 mg using a 1:1:1 allocation ratio. Randomization was stratified by underlying etiology of RVO (BRVO or CRVO). Regardless of initial treatment assignment, all patients who completed the double-masked phase (day 180) were eligible for treatment with DEX implant 0.7 mg at day 180 if BCVA was <84 letters (20/20) or retinal thickness was >250 μm in the central 1-mm macula subfield as measured by OCT3 (Stratus OCT, Carl Zeiss Meditech, Dublin, CA) and, in the investigator’s opinion, the procedure would not put the patient at significant risk. Eyes were evaluated for treatment at day 180 before unmasking. The treatment protocol (available at http://aaojournal.org) was standard for intravitreal injections.

Outcome Measures

Patients were evaluated at baseline and at 1, 7, 30, 60, 90, and 180 days after study treatment. The primary outcome at 12 months for the 6-month, open-label extension was safety. Safety parameters included AEs, IOP, slit-lamp biomicroscopy, and ophthalmoscopy. The presence of nuclear, cortical, and posterior subcapsular lens opacities was evaluated during the slit-lamp examination and assessed using standardized photographs. Secondary outcome measures included BCVA measured using a standardized Early Treatment Diabetic Retinopathy Study protocol and central subfield retinal thickness measured using OCT. Similar to the double-masked phase, visual acuity analyses in the open-label extension included the proportion of eyes with at least a 15-letter improvement from baseline, the proportion of eyes exhibiting ≥15 letters of worsening from baseline BCVA, and the mean change from baseline BCVA. For the OCT analysis, images were obtained from each study eye after pupil dilation by a certified operator using either an OCT2 (Carl Zeiss Meditech; 1 site only) or OCT3 (Stratus OCT, Carl Zeiss Meditech; all other sites) system.

Data Analysis and Statistical Methods

Results in the open-label extension were analyzed for all patients according to the actual treatment received: DEX implant 0.7 mg at day 0 and day 180 (retreated DEX 0.7/0.7 group); DEX implant 0.35 mg at day 0 and DEX implant 0.7 mg at day 180 (retreated DEX 0.35/0.7 group); sham at day 0 and DEX implant 0.7 mg at day 180 (DEX delayed-treatment group); DEX implant 0.7 mg at day 0 only (single-treatment DEX 0.7 group); DEX implant 0.35 mg at day 0 only (single-treatment DEX 0.35 group); or sham at day 0 only (untreated group). A subpopulation analysis based on RVO diagnosis (BRVO or CRVO) was also performed for key outcome measures. The single treatment and untreated groups included patients who did not complete the initial treatment period (discontinued before day 180), as well as patients who were not treated at day 180 because of failure to qualify for a second injection or other reasons. The safety population of all patients who received treatment at baseline was used for analysis. The last observation carried forward method was used to replace missing values in the efficacy analyses.

Summary statistics were calculated for all safety parameters and for efficacy parameters including the proportion of patients with a BCVA improvement or worsening of ≥15 letters from baseline and the change in BCVA and retinal thickness scores from baseline. Differences in the incidence of AEs and cataract were tested among the retreated and delayed treatment groups and among the single-treatment and untreated groups with the Pearson chi-square test or Fisher exact test. This report focuses on results with DEX implant 0.7 mg because this is the marketed, approved dose.

Results

Figure 1 illustrates the flow of patients through the 12-month study. A total of 1256 patients received a first injection with either DEX implant 0.7 mg (n = 421), DEX implant 0.35 mg (n = 412), or sham (n = 423) at the start of the study. At day 180, 1196 of the patients completed the initial double-masked phase of the study, and 997 of the study eyes received open-label DEX implant 0.7 mg. Of these 997 eyes, 99% met the visual acuity or retinal thickness criteria for retreatment, whereas 1% met neither of these criteria and should not have been treated. This was the second DEX implant injection for 341 patients treated with DEX implant
0.7 mg at baseline (retreated DEX 0.7/0.7 group) and for 329 patients treated with DEX implant 0.35 mg at baseline (retreated DEX 0.35/0.7 group), and the first injection for 327 patients treated with sham at baseline (DEX delayed treatment group). The remaining 199 patients seen at day 180 (60 treated with DEX implant 0.7 mg at baseline, 67 treated with DEX implant 0.35 mg at baseline, and 72 treated with sham at baseline) were entered into the open-label phase of the study for follow-up without receiving further treatment. These patients, along with patients who discontinued from the same study arms before day 180, comprised the single-treatment DEX 0.7 group, the single-treatment DEX 0.35 group, and the untreated group, respectively.

Study completion rates for the patients who received open-label DEX implant were high, with 5% of patients in the retreated and delayed-treatment groups discontinuing the study during the open-label phase (Table 2). Patients in the single-treatment and untreated groups were not treated with DEX implant at day 180 for the reasons listed in Table 3. Approximately 23% of these patients had discontinued the study before day 180, and another 10% discontinued the study during the open-label phase (Table 3). Of the 199 patients who were seen at day 180 but did not receive open-label DEX implant treatment, 172 (86%) completed the study (Table 3). Patient demographics and baseline characteristics are listed in Table 4 (available online at http://aaojournal.org).

### Safety Analysis

Table 5 summarizes the occurrence of AEs in the 12-month study. The incidence of serious AEs was similar across all treatment groups. Almost all of the AEs that the investigators considered to be possibly

---

**Table 2. Patient Disposition in the Retreated and Delayed-Treatment Groups**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Retreated DEX Implant 0.7/0.7 (n = 341)</th>
<th>Retreated DEX Implant 0.35/0.7 (n = 329)</th>
<th>Delayed Treatment Sham/DEX Implant 0.7 (n = 327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued before day 360</td>
<td>11 (3.2%)</td>
<td>13 (4.0%)</td>
<td>14 (4.3%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>4 (1.2%)</td>
<td>3 (0.9%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Administrative</td>
<td>1 (0.3%)</td>
<td>7 (2.1%)</td>
<td>6 (1.8%)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>3 (0.9%)</td>
<td>2 (0.6%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Completed study at day 360</td>
<td>330 (96.8%)</td>
<td>316 (96.0%)</td>
<td>313 (95.7%)</td>
</tr>
</tbody>
</table>

DEX implant = dexamethasone intravitreal implant.
related to treatment occurred in the study eye. Four serious AEs in
patients treated with DEX implant were considered to be related to
treatment (3 elevated IOP and 1 retinal detachment).

The 12-month AE profile associated with repeated DEX implant
treatment was similar to the AE profile associated with a single DEX
implant treatment in the initial 6-month, masked treatment phase of
the study. During the open-label extension, as in the initial 6-month
study, the most common AEs after DEX implant treatment were
conjunctival hemorrhage associated with the injection and increases in
IOP. The 12-month incidence of conjunctival hemorrhage was 24.9%
(85/341) in the retreated DEX 0.7/0.7 group, 22.5% (74/329) in the
reverted DEX 0.7/0.7 group, 22.3% (73/327) in the delayed-
treatment group. There were no reports of endophthalmitis in any of
the treatment groups. With the exception of cataract, there were no
statistically significant differences in the incidence of ocular AEs
between patients who received 2 injections of DEX implant and
patients who had been treated initially with sham and received DEX
implant at day 180 only.

Most of the phakic study eyes (80.1% and 83.0% in the retreated
DEX 0.7/0.7 and 0.35/0.7 groups, 74.7% in the delayed treatment
group, 68.2% and 51.3% in the single-treatment DEX 0.7 and 0.35
groups, and 65.9% in the untreated group) had lens opacity at baseline
before study treatment. During the study, cataract AEs (subcapsular,
cortical, or nuclear) were reported in 29.8% (90/302) of phakic study
eyes in the single-treatment DEX 0.7 group, 22.5% (74/329) in the
reverted DEX 0.35/0.7 group, and 10.5% (31/296) of phakic study
eyes in the retreated DEX 0.7/0.7 group, 19.8% (56/283) of phakic
study eyes in the delayed treatment group (P < 0.001). The 12-
month incidence of cataract AEs in phakic study eyes in the single-
treatment DEX implant 0.7 mg and 0.35 mg groups and in the untreated
group were 7.6% (5/66), 7.7% (6/78), and 5.7% (5/88), respectively (P =

Table 3. Patient Disposition in the Single-Treatment and Untreated Groups

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Single Treatment</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEX implant 0.7/None (n = 80)</td>
<td>DEX implant 0.35/None (n = 83)</td>
</tr>
<tr>
<td>Discontinued before day 180</td>
<td>20 (25.0%)</td>
<td>16 (19.3%)</td>
</tr>
<tr>
<td>Reason</td>
<td>Adverse event</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td></td>
<td>7 (8.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>8 (9.6%)</td>
<td>3 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>8 (8.3%)</td>
<td>4 (4.2%)</td>
</tr>
<tr>
<td>Reason</td>
<td>Safety concerns</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>10 (12.5%)</td>
<td>18 (22.5%)</td>
</tr>
<tr>
<td></td>
<td>17 (20.5%)</td>
<td>16 (19.3%)</td>
</tr>
<tr>
<td></td>
<td>9 (4.9%)</td>
<td>19 (22.0%)</td>
</tr>
<tr>
<td>Reason</td>
<td>Adverse event</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>1 (1.0%)</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Completed study at day 360</td>
<td>53 (66.2%)</td>
<td>57 (68.7%)</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; DEX implant = dexamethasone intravitreal implant.

Table 5. Incidence of Adverse Events (AE) During the 12-Month Study

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Retreated</th>
<th>Delayed-treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEX Implant (n = 341)</td>
<td>DEX Implant (Sham/0.7) (n = 327)</td>
<td></td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>291 (85.3)</td>
<td>287 (87.2)</td>
<td>262 (80.1)</td>
</tr>
<tr>
<td>Any AE considered treatment related, n (%)</td>
<td>216 (63.3)</td>
<td>205 (62.3)</td>
<td>163 (49.8)</td>
</tr>
<tr>
<td>Study eye ocular AE, n (%)</td>
<td>265 (77.7)</td>
<td>261 (79.3)</td>
<td>235 (71.9)</td>
</tr>
<tr>
<td>Study eye ocular AE considered treatment related, n (%)</td>
<td>216 (63.3)</td>
<td>205 (62.3)</td>
<td>162 (49.5)</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>32 (9.4)</td>
<td>27 (8.2)</td>
<td>35 (10.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Single Treatment</th>
<th>Untreated</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEX Implant (0.7/None) (n = 80)</td>
<td>DEX Implant (0.35/None) (n = 83)</td>
<td>Untreated (Sham/None) (n = 96)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>65 (81.3)</td>
<td>63 (75.9)</td>
<td>55 (57.3)</td>
</tr>
<tr>
<td>Any AE considered treatment related, n (%)</td>
<td>42 (52.5)</td>
<td>40 (48.2)</td>
<td>10 (10.4)</td>
</tr>
<tr>
<td>Study eye ocular AE, n (%)</td>
<td>57 (71.3)</td>
<td>51 (61.4)</td>
<td>46 (47.9)</td>
</tr>
<tr>
<td>Study eye ocular AE considered treatment related, n (%)</td>
<td>42 (52.5)</td>
<td>40 (48.2)</td>
<td>10 (10.4)</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>8 (10.0)</td>
<td>9 (10.8)</td>
<td>10 (10.4)</td>
</tr>
</tbody>
</table>

DEX implant = dexamethasone intravitreal implant.
Cataracts were extracted at the investigator’s and patient’s discretion in a total of 11 study eyes: 4 eyes (1.3% of phakic eyes) in the retreated DEX 0.7/0.7 group, 5 eyes (1.8% of phakic eyes) in the retreated DEX 0.35/0.7 group, 1 eye (1.3% of phakic eyes) in the single-treatment DEX implant 0.35 group, and 1 eye (1.1% of phakic eyes) in the untreated group. There were no cataract extractions in study eyes in the single-treatment DEX 0.7 group or the delayed-treatment group.

Increases in IOP were most commonly observed in study eyes at visits 60 days after treatment with DEX implant (Fig 2). In the retreated DEX 0.7/0.7 group, an IOP increase of ≥10 mmHg from baseline was seen in 12.6% of study eyes at 60 days after the first DEX implant injection and 15.4% of study eyes at 60 days after the second DEX implant injection. Overall, 32.8% of study eyes in the retreated DEX 0.7/0.7 group had at least a 10-mmHg increase in IOP from baseline at some point in the 12-month study. In almost all cases, the increase in IOP had resolved by 180 days after DEX implant treatment, with most of the increases in IOP successfully managed with observation or topical IOP-lowering medication. Use of IOP-lowering medication in study eyes during the double-masked and open-label phases of the study is summarized in Table 6 (available online at http://aaojournal.org). In the initial treatment group that received DEX implant 0.7 mg at baseline, 25.5% of patients began treatment with IOP-lowering medication during the masked phase of the study, and in the subgroup that qualified for retreatment and received a second injection of DEX implant 0.7 mg at day 180, an additional 10.3% of patients began treatment with IOP-lowering medication during the open-label phase of the study. A laser or surgical procedure to reduce IOP was required for 14 study eyes—6 in the retreated DEX implant groups (including 1 eye with neovascular glaucoma treated with panretinal photocoagulation), 2 in the delayed-treatment group (including 1 eye treated with iridotomy in the masked phase of the study, before DEX implant treatment), 6 in the single-treatment groups (including 3 eyes with neovascular glaucoma also treated with panretinal photocoagulation), and 0 in the untreated group.

Visual Acuity

Among patients who received 2 treatments with DEX implant 0.7 mg, BCVA improvements were similar after the first and second injections. Overall, as well as in the subgroups of study eyes diagnosed with BRVO and CRVO, the peak improvement in mean BCVA was approximately 10 letters and occurred at 60 days after each injection (Fig 3). At least a 15-letter improvement in BCVA from baseline was seen in up to 30% of eyes in the DEX 0.7/0.7 group at visits during the masked phase of the study (the first 6 months) and in up to 32% of eyes in the DEX 0.7/0.7 group at visits during the open-label phase of the study (the second 6 months; Fig 4). At least a 10-letter improvement in BCVA from baseline was seen in up to 55% of eyes in the DEX 0.7/0.7 group and in up to 46% of eyes in the delayed-treatment group at visits during the open-label phase of the study (Fig 5, available online at http://aaojournal.org).

Patients who had delayed treatment (after initial treatment with sham, they received DEX implant 0.7 mg at the start of the open-label phase of the study) never matched the improvement of those treated earlier in the disease process: the peak improvement in mean BCVA was approximately 3 letters during the masked phase of the study (after sham treatment) and approximately 7 letters during the open-label phase of the study (after DEX implant treatment; Fig 3). Up to 27% of patients in the delayed-treatment group had at least a 15-letter improvement in BCVA from baseline at visits during the open-label phase of the study (Fig 4).

Retinal Thickness

For patients treated with the DEX implant who qualified for retreatment and received DEX implant 0.7 mg at the start of the open-label extension, the second injection of DEX implant reduced central retinal thickness in the central 1-mm subfield similarly to the first injection (Table 7, available online at
At 90 days after open-label treatment with DEX implant 0.7 mg, the mean (standard deviation) reduction in retinal thickness from baseline was 263 (219) μm and 263 (217) μm in patients who received their second injection of DEX implant (retrieved DEX 0.35/0.7 and 0.7/0.7 groups, respectively) and 267 (206) μm in patients who received their first injection of DEX implant (DEX delayed-treatment group).

Discussion

Reinjection with DEX implant 0.7 mg in patients who met retreatment criteria for macular edema owing to BRVO or CRVO in this study was safe and well-tolerated over 12 months. The safety profile after a second treatment with DEX implant 0.7 mg was generally similar to that seen after the first treatment, except that more cataract progression occurred in eyes that received retreatment with 0.7 mg DEX implant. Steroid-induced increases in IOP after each DEX implant treatment were predictable and typically were controlled with topical IOP-lowering medication. As this was a safety study, few analyses of efficacy were performed. Nonetheless, efficacy findings in the study were also favorable, with improvements in BCVA and central retinal thickness after a second treatment with DEX implant 0.7 mg similar to those seen after the first treatment.

During the 12-month study, serious treatment-related AEs were very infrequent (4/1830 DEX implants). Retinal tears and retinal detachments were rare and did not differ among the treatment groups; there were no cases of endophthalmitis.
incidence of ocular AEs was similar in the retreated groups that received 2 DEX implants (at days 0 and 180) and the delayed-treatment group that received 1 DEX implant (at day 180 only) with the exception of cataract. The difference in cataract incidence could be due to the cumulative effects of 2 treatments with DEX implant or to a slow development of cataracts after the first injection. Increases in IOP after a second treatment with DEX implant 0.7 mg were similar to those after the first injection, as seen both in the percentage of patients who had substantial increases in IOP from baseline and in the time course of IOP elevations (Fig 2). The number of patients with elevated IOP peaked at 60 days after each treatment. Although patient initiation of IOP-lowering medication during the double-masked and open-label phases of the study was recorded, the duration of medication use varied, confounding the analysis of IOP increases after the second injection. Nonetheless, the results suggest that there is no progressive increase in the number of patients with elevated IOP after repeated treatment. Only an additional 10.3% of patients initiated IOP-lowering medication after their second DEX implant 0.7 mg treatment, and few patients who received either 1 or 2 treatments with DEX implant required laser or surgical treatment to control their IOP.

Cataract and increases in IOP are both expected side effects after intraocular corticosteroid treatment. In the Standard Care versus Corticosteroid for Retinal Vein Occlusion 12-month clinical comparisons of the effects of triamcinolone with standard care in patients with BRVO and CRVO, cataract surgery was required in 5.3% (4/76) of phakic CRVO eyes and 3.6% (4/110) of phakic BRVO eyes treated with intravitreal triamcinolone (4 mg). By comparison, in the present study, cataract extractions were performed in 1.3% (4/302) of phakic RVO eyes over the course of 12 months in the study group that received 2 treatments with DEX implant 0.7 mg. Furthermore, in the Standard Care versus Corticosteroid for Retinal Vein Occlusion study, increases in IOP from baseline of ≥10 mmHg were observed in 8.9% (18/202) of eyes at the month 12 visit, and 3.5% (7/202) of eyes had IOP >35 mmHg at that visit (Allergan, data on file), whereas in the present study, only 0.9% (3/324) of eyes treated with 2 injections of DEX implant had an increase in IOP from baseline of ≥10 mmHg at month 12, and no eyes had an IOP >35 mmHg at that visit. The beneficial effects of treatment on vision and macular thickening also were similar after the first and second injection of DEX implant 0.7 mg. The percentage of patients achieving at least a 15-letter improvement in BCVA, the percentage of patients experiencing at least a 15-letter worsening in BCVA, and the mean change in BCVA after a second treatment with DEX implant 0.7 mg were all very similar to those seen after the first treatment. Improvements in retinal thickness after a second treatment with DEX implant 0.7 mg were also similar to those seen after the first treatment.

The study included 327 patients who were treated initially with sham and did not receive a first DEX implant until the beginning of the open-label phase (delayed-treatment group). In this group, the mean improvement in BCVA did not seem to be as robust as that seen in patients who received their first DEX implant 6 months earlier in the study (Fig 3), perhaps suggesting that delaying treatment in eyes with macular edema owing to RVO may decrease the ability of patients to benefit from treatment. However, the requirement that patients qualify for treatment at day 180 to be included in the delayed-treatment group may also account in part for the apparent reduction in BCVA response in this group, as any patients treated with sham whose macular edema resolved spontaneously would not qualify for open-label DEX implant treatment. Further analyses of the impact of delay in treatment from this dataset are forthcoming.

Evaluation of these results must be performed in the context of the natural history data from the study, showing that 43 (10.1%) of the eyes treated with sham injections at baseline recovered BCVA to the 20/20 level at 6 months, with resolution of edema centrally to ≤250 μm. Further study is needed to address the important issue of predicting which patients with macular edema owing to RVO can most benefit from DEX implant treatments and which patients might improve with no treatment. Knowledge that an individual eye has a high degree of likelihood of improving to 20/20 visual acuity with DEX implant treatment, or conversely, with no treatment, would certainly help to guide clinicians and patients in their management decisions.

Eyes with macular edema owing to either BRVO or CRVO were included in this study because the study purpose was to evaluate DEX implant in the treatment of retinal venous occlusive disease. Although BRVO and CRVO differ in anatomic location of the vascular blockage, severity, and prognosis, their pathogenetic risk factors and the mediating factors that produce secondary macular edema are very similar. Pre-planned subgroup analyses of efficacy in eyes with BRVO and CRVO confirmed previous observations that untreated eyes with CRVO have a poorer visual prognosis than untreated eyes with BRVO, and further showed that DEX implant treatment has beneficial effects on vision in both BRVO and CRVO (Fig 3). All safety analyses were performed in the total safety population to improve the power of the study to identify any safety concerns.

A key weakness of this study is that it does not directly address the question of the optimum retreatment interval for DEX implant 0.7 mg. The time course and magnitude of the response to each treatment suggests that some eyes were undertreated and that physicians may want to evaluate their patients for retreatment earlier than 180 days. Studies of DEX implant injections given “as-needed” over longer periods of time, possibly in combination with other drugs, will be required to help establish optimum treatment protocols. Furthermore, the study provided only limited information regarding the 12-month safety and efficacy of a single DEX implant injection because most of the patients in the study received open-label DEX implant treatment at day 180. In particular, our estimates of the 12-month incidence of cataract associated with a single DEX implant treatment could have been low, because the single-treatment and untreated groups included patients who were not followed in the last 6 months of the study. Additional study is needed to evaluate the effect of DEX implant single treatment and retreatment on cataract progression over longer periods of follow-up.

In conclusion, among patients with macular edema owing to BRVO or CRVO, treatment with 1 or 2 doses of DEX implant 0.7 mg at a 6-month interval demonstrated a favorable
safety and tolerability profile over 12 months of follow-up. The results demonstrated that, for most patients, DEX implant treatment can be repeated with no new safety concerns after the second treatment with regard to IOP increases, although cataract progression does seem to increase. Acute treatment-related serious AEs, including vitreous hemorrhage, endophthalmitis, and retinal detachment, are extremely rare after both initial injection and reinjection. For patients who received a second treatment with DEX implant, the second treatment was as effective as the first treatment in improving BCVA and central retinal thickness, although patients randomized to initial treatment with either dose of dexamethasone had better visual outcomes than those randomized to sham treatment.

Acknowledgments. Amy Lindsay, PhD, and Kate Ivins, PhD, provided professional writing assistance (funded by Allergan, Inc.) with the preparation of the manuscript but did not meet authorship criteria.

References


Footnotes and Financial Disclosures

Originally received: January 14, 2011.
Final revision: May 9, 2011.
Accepted: May 10, 2011.

1 Wills Eye Institute, Philadelphia, Pennsylvania.
2 University Vita Salute, Hospital San Raffaele, Milan, Italy.
3 Vision Institute, Federal University of São Paulo, São Paulo, Brazil.
4 Stanford University, Stanford, California.
5 University of Sydney, Sydney, Australia.
6 Ophthalmic Consultants of Boston, Boston, Massachusetts.
7 Tel Aviv Medical Center, Tel Aviv, Israel.
8 Asan Medical Center, Seoul, South Korea.
9 Allergan, Inc., Irvine, California.


Financial Disclosure(s):
The authors have made the following disclosures:
Julia A. Haller - Consultant - Allergan, Genentech, Regeneron.
Francesco Bandello - Consultant - Allergan, Bayer, Novartis, Thea, Pfizer, Alcon.
Rubens Belfort Jr - Consultant - Alcon, Allergan.
Mark S. Blumenkranz - Consultant - Allergan, Genentech; Equity Owner - Optimedica.
Mark Gillies - Consultant - Allergan, Genentech, Novartis, Pfizer; Lecture Fees - Allergan; Research Support - Allergan, Novartis.
Jeffrey Heier - Consultant, Research Support - Alimera, Allergan, Genentech, Regeneron.
Anat Loewenstein - Consultant - Allergan.
Young Hee Yoon - Consultant - Allergan, Bayer, Novartis; Lecture Fees - Alcon, Allergan, Bayer.
Jenny Jiao - Employee - Allergan.
Xiao-Yan Li - Employee - Allergan.
Scott M. Whitcup - Employee, Equity Owner - Allergan.
Sponsored by Allergan, Inc. The sponsor participated in the design of the study, conducting the study, data management, data analysis, interpretation of the data, and the preparation, review, and approval of the manuscript.

Correspondence:
Julia A. Haller, MD, Wills Eye Institute, 840 Walnut Street, Suite 1510, Philadelphia, PA 19107. E-mail: jhalter@willsye.org.

*The GENEVA (Global Evaluation of implaNable dExamethasone in retinal Vein occlusion with macular edema) Study Group Investigators are listed online at http://aaojournal.org. The GENEVA Study Group Writing Committee: Francesco Bandello, Rubens Belfort Jr, Mark Gillies, Julia A. Haller (Chair), Jeff Heier, Anat Loewenstein, Mark S. Blumenkranz, Young Hee Yoon, Joanne Li, and Scott M. Whitcup.