Real-World Assessment of Dexamethasone Intravitreal Implant in DME: Findings of the Prospective, Multicenter REINFORCE Study

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BACKGROUND AND OBJECTIVE: Dexamethasone intravitreal implant (DEX) (Ozurdex; Allergan plc, Dublin, Ireland) is approved for the treatment of diabetic macular edema (DME). This study assessed the real-world effectiveness, safety, and reinjection interval of DEX in adult patients with DME.

PATIENTS AND METHODS: This was a phase 4, prospective, multicenter (18 U.S. sites), observational study.

RESULTS: The study population comprised 177 patients (180 eyes; 93.8% previously treated). Baseline mean best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were 54.4 letters and 424.6 µm, respectively. DEX was administered as monotherapy or with other DME therapy (55%/45%). The mean reinjection interval was 5.0 months. Mean maximum BCVA change from baseline after the first three DEX injections was +9.1 letters, +7.7 letters, and +7.0 letters, respectively ($P < .001$); 36.0% of eyes achieved 15-letter or greater BCVA improvement. Mean maximum CRT change from baseline was −137.7 µm ($P < .001$).

CONCLUSION: DEX used alone or with other DME therapy improved visual and anatomic outcomes in DME patients in clinical practice, with no new safety concerns.

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INTRODUCTION

Diabetic macular edema (DME) is an increasingly frequent cause of visual impairment throughout the world because of the rising global prevalence

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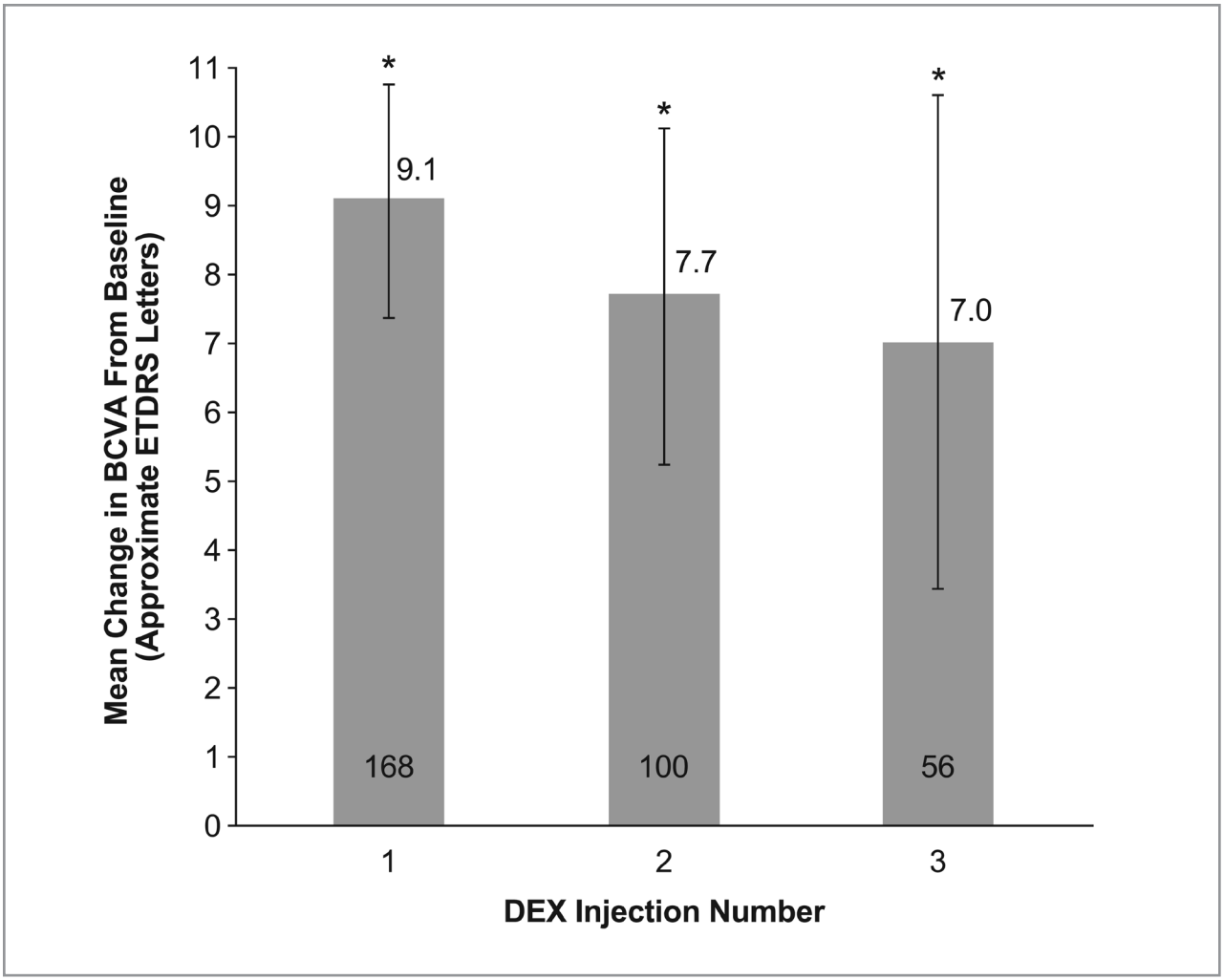

Figure 1. Mean change in best-corrected visual acuity (BCVA) from baseline after each dexamethasone intravitreal implant (DEX) injection. When BCVA measurements were available from more than one visit after an injection, the value from the visit showing best improvement in BCVA was used for analysis. Numbers within bars indicate the number of patients with available data. Error bars indicate 95% confidence interval of the mean. *$P < .001$.

of diabetes.[1] In the U.S., it has been estimated that 3.8% of adults ages 40 years and older with diabetes mellitus have DME.[2] A critical challenge is to address the refractory nature of the disease. Since the 1980s, standard of care for DME had been focal and/or grid laser photocoagulation of leaking microaneurysms and areas of retinal thickening to reduce the rate of further loss in vision.[3] However, within the past few years, treatment options have expanded with the increasing use of intravitreal vascular endothelial growth factor (VEGF) inhibitors and corticosteroids to reduce retinal thickening and improve vision in patients with DME.[4]

DME exhibits features of a chronic, localized, inflammatory response, including expression of a complex array of cytokine growth factors and proinflammatory mediators, recruitment and activation of leukocytes, and expression of transcription factors essential for cellular proliferation and apoptosis.[5,6] Corticosteroids are a rational approach to DME treatment because they have anti-inflammatory effects and inhibit multiple pathways involved in the pathophysiology of DME.[7] Effective intravitreal corticosteroid treatment of posterior segment disease requires use of a sustained-release delivery system to offset the short intravitreal half-life of corticosteroids.[8] Dexamethasone intravitreal implant (DEX) (Ozurdex; Allergan plc, Dublin, Ireland) provides sustained release of dexamethasone to the retina, thereby reducing the need for frequent injections.[9] In two large, multicenter, phase 3 trials (the MEAD study), a mean of four to five intravitreal injections of DEX 0.7 mg or

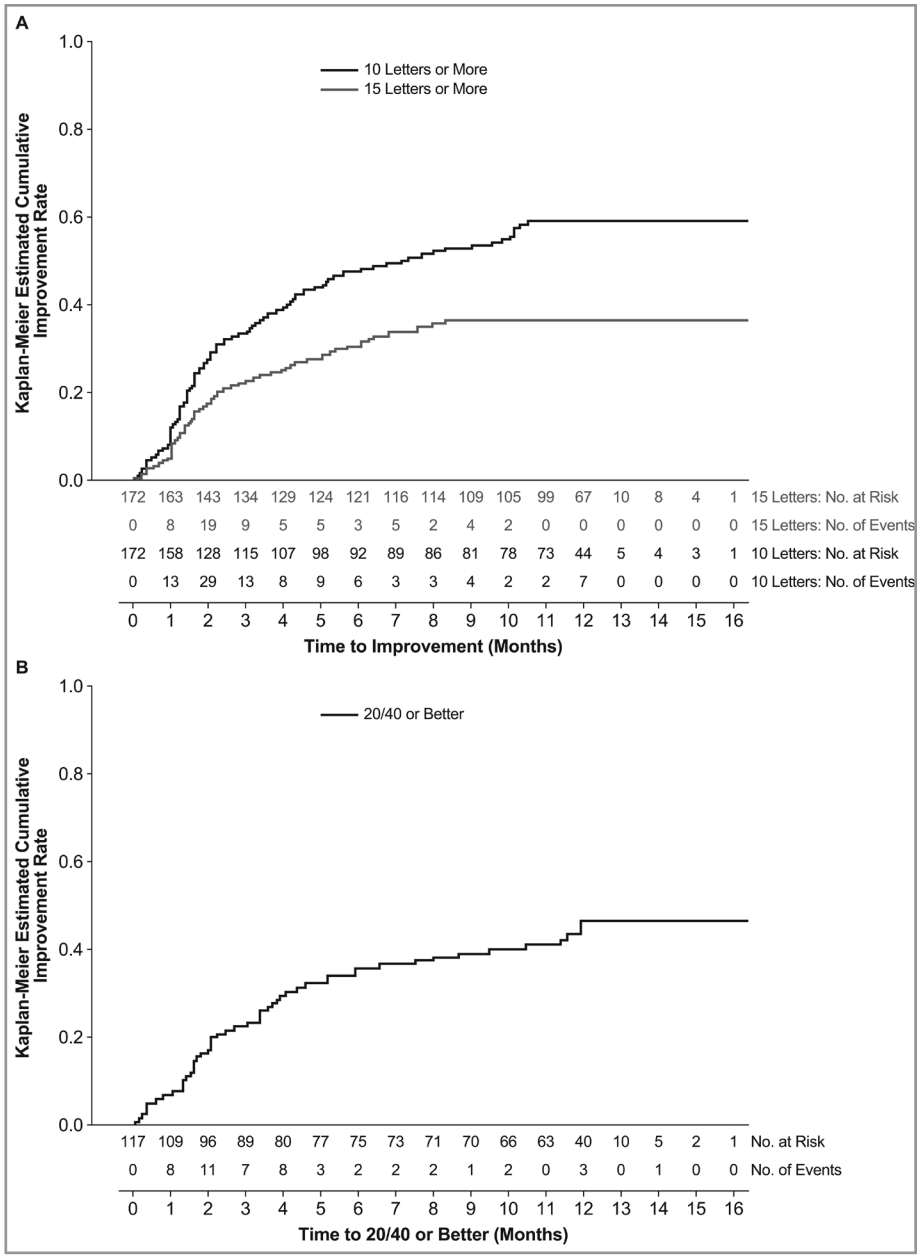

Figure 2. Kaplan-Meier analysis of time to improvement in best-corrected visual acuity (BCVA). (A) Time to improvement in BCVA from baseline of 10 or more, or 15 or more, approximate ETDRS letters. (B) Time to improvement in BCVA to 20/40 or better (for eyes with baseline BCVA worse than 20/40).

0.35 mg across a period of 3 years produced clinically significant visual and anatomic improvements in patients with DME.[10] These findings provided the basis for the U.S. Food and Drug Administration approval of DEX 0.7 mg in 2014 for the treatment of DME.

Currently, there is limited information relating to injection intervals and treatment outcomes with DEX as used in clinical practice in patients with DME. Therefore, the objective of the present study was to assess the real-world effectiveness and safety of DEX 0.7 mg, used either as monotherapy or with other DME treatments, in treatment-naïve and previously treated patients with DME.

PATIENTS AND METHODS

Study Design

REINFORCE was a phase 4, prospective, multicenter, observational study conducted between August 13, 2014, and May 19, 2016, at 18 sites in the United States. The study protocol did not provide criteria for patient selection or give guidance on when or how to use DEX. All decisions regarding treatment and procedures were made at the discretion of the treating physicians in accordance with their usual clinical practice. No specific treatment beyond the initial DEX injection was

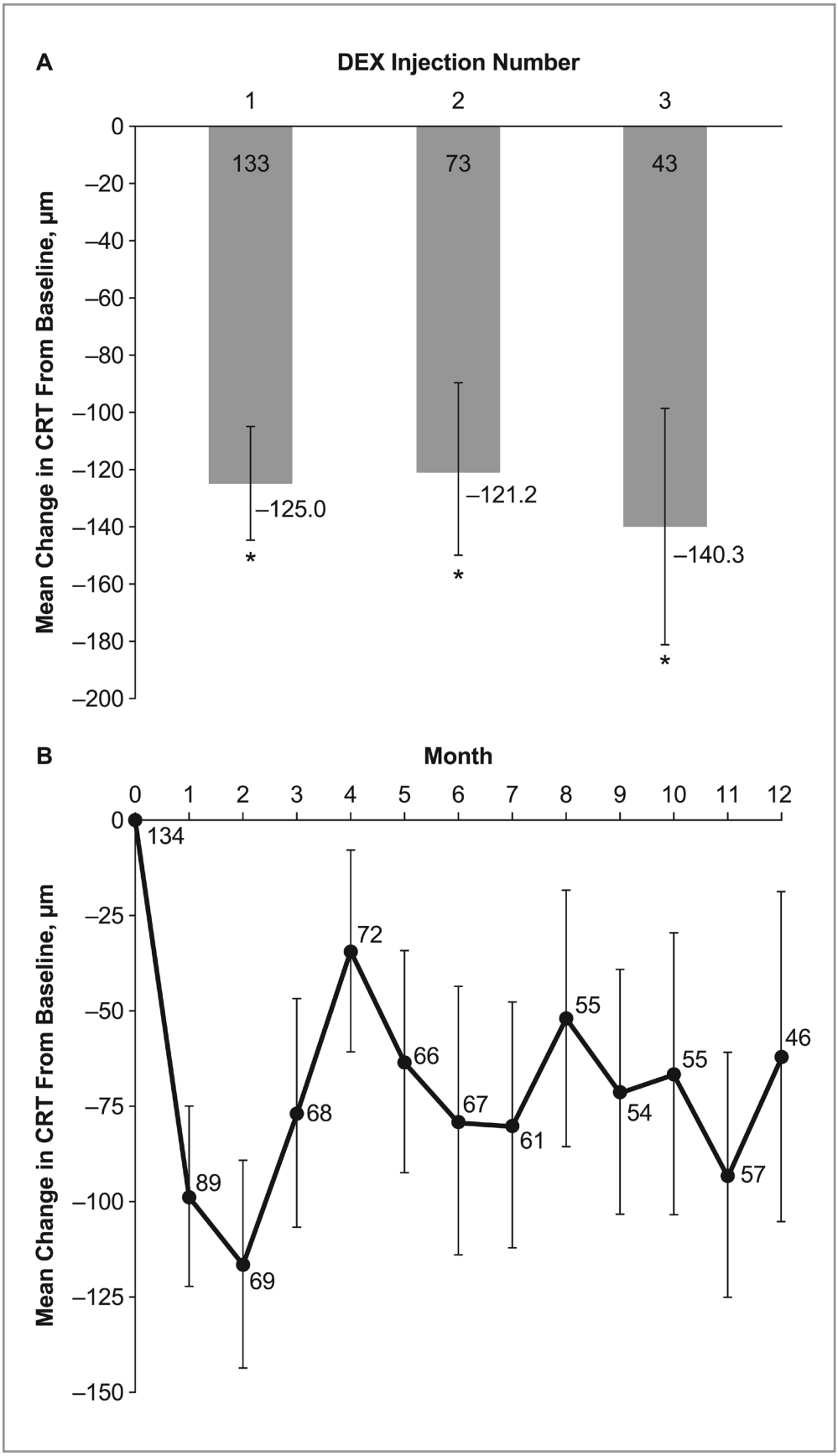

Figure 3. Mean maximum change in central retinal thickness (CRT) from baseline (A) after each dexamethasone intravitreal implant (DEX) injection and (B) by month after the initial DEX injection. Numbers within bars or by data points indicate the number of patients with available data. Error bars indicate 95% confidence interval of the mean. *$P < .001$.

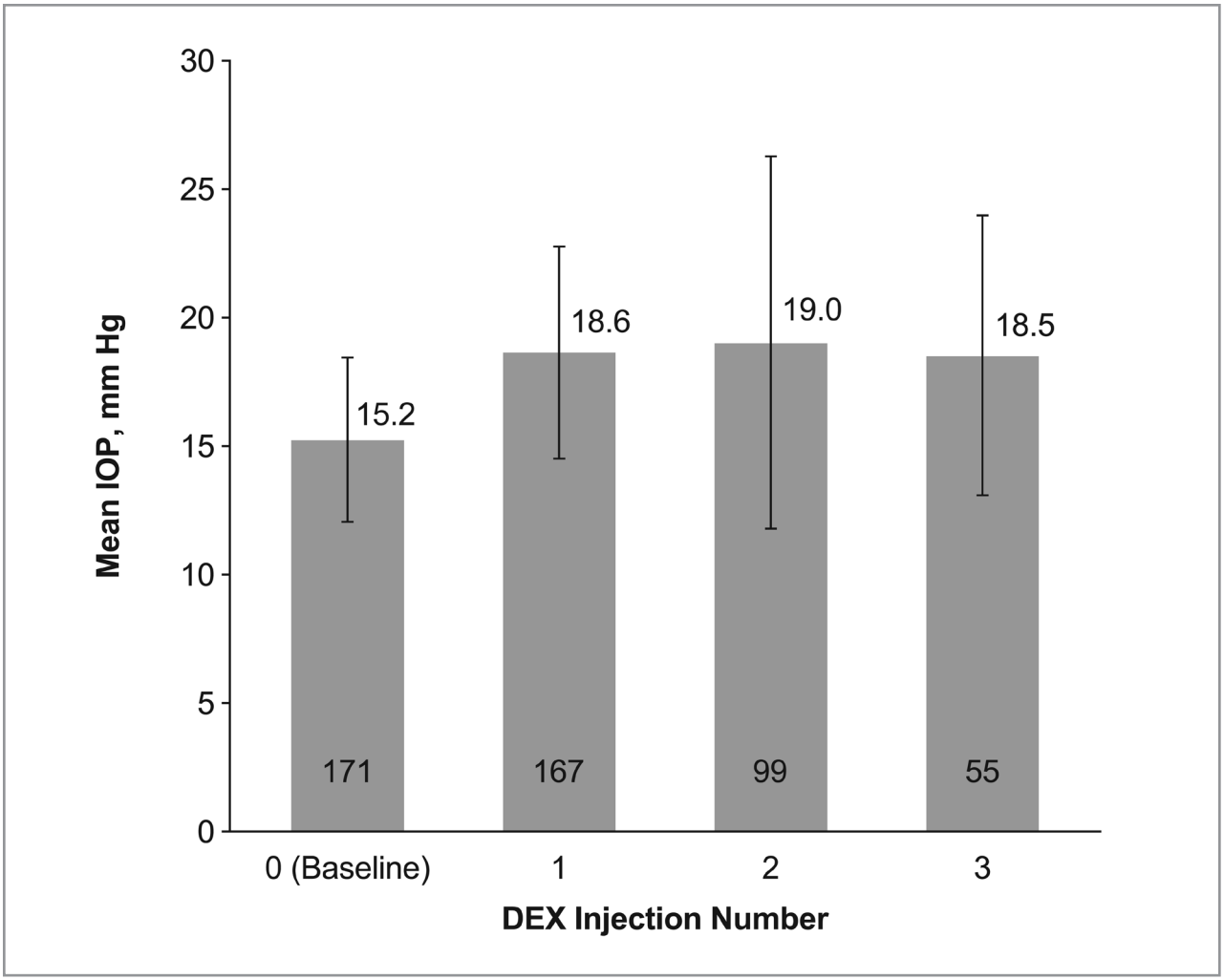

Figure 4. Mean intraocular pressure (IOP) after each dexamethasone intravitreal implant (DEX) injection. Numbers within bars indicate the number of patients with available data. Error bars indicate the standard deviation.

mandated. The study protocol was approved by an institutional review board at each site, and the study was conducted in accordance with the International Council for Harmonization Good Clinical Practice Guideline. All participating patients provided written informed consent. The study is registered at www.ClinicalTrials.gov with the identifier NCT02188173.

Patients

Patients enrolled in the study were 18 years of age or older with DME in the study eye that was treated with DEX following its regulatory approval. Both eyes of a patient could be included in the study if both eyes had DME that was treated with DEX. Patients were excluded for concurrent participation in a clinical trial that required treatment or use of an investigational agent.

Procedures and Study Endpoints

Data recorded per the investigator's standard practice were collected at participating sites from the visit at the time of the patient's first DEX injection and all subsequent visits up to 1 year after the first DEX injection. Data collected included medical and ophthalmic history and demographics (at the first injection visit only), intravitreal injections and other procedures for treatment of DME, Snellen best-corrected visual acuity (BCVA), optical coherence tomography (OCT), fluorescein angiography, intraocular pressure (IOP), use of concomitant IOP-lowering medications, ocular surgeries, and adverse events (AEs).

The primary effectiveness endpoints were the mean maximum BCVA change (best improvement) from baseline after each DEX injection, the percentage of eyes with improvement in BCVA of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and the

TABLE 1

Baseline Characteristics of Patients

Characteristic	Patient Population (n = 177)
Mean Age (SD), Years	67.0 (9.9)
Range	38–90
Gender, n (%)	
Male	93 (52.5)
Female	84 (47.5)
Race, n (%)	
White	149 (84.2)
African-American	9 (5.1)
Asian	9 (5.1)
Other	10 (5.6)
Duration of Diabetes, Years	
≤15	84 (47.5)
>15	92 (52.0)
Not recorded	1 (0.6)
HbA1c, n (%)	
≤ 8%	30 (16.9)
>8%	6 (3.4)
Not recorded	141 (79.7)
History of Previous DME Treatment, n (%)	
Yes	166 (93.8)
Laser	63 (35.6)
No	11 (6.2)
History of Vitrectomy, n (%)	52 (29.4)
DME Perfusion Status, n (%)	
Nonischemic	113 (63.8)
Ischemic	8 (4.5)
Not applicable	53 (29.9)
Not recorded	3 (1.7)

SD = standard deviation; DME = diabetic macular edema; HbA1c = glycosylated hemoglobin

mean average improvement in BCVA from baseline during the study using an area-under-the-curve (AUC) approach. Key secondary endpoints included the mean number of DEX injections received by patients, the mean time between DEX injections, the mean maximum improvement in BCVA from baseline across all injections, the percentage of eyes with a 10-letter or greater improvement in BCVA from baseline, the time to BCVA improvement of 10 or more, 15 or more letters from baseline, and the mean change in central subfield retinal thickness (CRT) from baseline by OCT after each DEX injection. Exploratory outcomes included the percentage of study eyes that achieved 20/40 or better BCVA, the percentage of study eyes that achieved CRT of 300 µm or less, and the percentage of study eyes that achieved both 20/40 or better BCVA and CRT of 300 µm or less at the same visit. Safety outcomes included increases in IOP and the incidence of AEs.

Analysis

The intent-to-treat data set of all study eyes that were administered a DEX injection was used for the analysis of effectiveness outcomes, ocular surgeries

TABLE 2
Baseline Study Eye Characteristics

Characteristic	Study Eyes (n = 180)
Lens Status, n (%)	
Phakic	53 (29.4)
Pseudophakic	109 (60.6)
Aphakic	3 (1.7)
Not recorded	15 (8.3)
DME Duration, n (%)	
<1 year	62 (34.4)
≥1 year to ≤2 years	40 (22.2)
>2 years	78 (43.3)
Diabetic Retinopathy Severity, n (%)	
Mild	36 (20.0)
Moderate	39 (21.7)
Severe	38 (21.1)
Not recorded	67 (37.2)
Mean BCVA (SD), Approximate ETDRS Letters (n = 172)	54.4 (20.2)
Range	0–85
Snellen equivalent (range)	~20/80 (CF–20/20)
Mean CRT (SD), μm (n = 140)	424.6 (138.2)
Range	179–920

DME = diabetic macular edema; BCVA = best-corrected visual acuity; SD = standard deviation; ETDRS = Early Treatment Diabetic Retinopathy Study; CF = counting fingers; CRT = central subfield retinal thickness

and procedures, and IOP. AEs and use of IOP-lowering medications were analyzed in the safety population of all patients who were administered a DEX injection in one or both eyes.

Statistical analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC). Effectiveness data were summarized by DEX injection number and across all injection numbers, as well as by month and across all monthly post-baseline visits. In all CRT analyses and all BCVA analyses except the time to event analyses and the AUC analysis, if measurements were available from more than one visit after an injection or within a visit window, the measurement demonstrating the best outcome (greatest improvement from baseline) was used in the analysis. Snellen visual acuity measurements were converted to approximate ETDRS letters using the method described by Gregori et al.[11] Changes from baseline were analyzed with paired *t*-tests. Calculations of the 95% confidence interval (CI) for the percentage of study eyes used the exact binomial distribution. Time to BCVA and CRT improvement was estimated using Kaplan-Meier methods. Preplanned subgroup analysis of key efficacy parameters was performed for variables including baseline lens status, duration of DME, prior laser treatment for DME, prior vitrectomy, and pattern of DEX use. AEs were categorized by preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

No formal sample size calculation was performed. The planned enrollment was approximately 200 patients.

RESULTS

Patient Characteristics and Disposition

A total of 177 patients (180 study eyes; both eyes qualified in three patients) were enrolled at 18 U.S. sites. Patient demographics are summarized in Table 1. Most patients (84.2%) were white, 52.5% were male, and 59.3% were older than 65 years of age. Almost all patients (93.8%) had been treated previously for DME with intraocular pharmacotherapy and/or la-

TABLE 3

Subgroup Analysis of Key Efficacy Parameters

	Mean ± SD Maximum Improvement in BCVA After Each Injection, Letters			Mean ± SD Maximum Improvement in CRT Across All Months, µm
Subgroup	**Injection 1**	**Injection 2**	**Injection 3**	
Baseline Lens Status				
Phakic	8.6 ± 11.5 (n = 52)	8.5 ± 14.8 (n = 29)	5.2 ± 17.8 (n = 13)	–120.8 ± 113.5 (n = 42)
Pseudophakic	9.4 ± 11.6 (n = 100)	7.4 ± 11.1 (n = 60)	7.6 ± 12.4 (n = 37)	–142.4 ± 123.9 (n = 85)
Duration of DME				
<1 year	9.7 ± 8.9 (n = 62)	7.8 ± 11.0 (n = 36)	0.5 ± 9.2 (n = 15)	–145.0 ± 121.4 (n = 48)
1–2 years	8.9 ± 12.5 (n = 36)	10.1 ± 10.5 (n = 19)	9.4 ± 10.8 (n = 14)	–118.7 ± 110.0 (n = 31)
>2 years	8.6 ± 12.3 (n = 70)	6.5 ± 13.9 (n = 45)	9.3 ± 15.6 (n = 27)	–142.1 (124.1) (n = 55)
Prior Laser Treatment for DME				
Yes	10.1 ± 13.6 (n = 56)	10.3 ± 13.0 (n = 34)	10.7 ± 14.7 (n = 21)	–134.9 ± 115.6 (n = 35)
No	8.5 ± 9.7 (n = 112)	6.3 ± 11.7 (n = 66)	4.8 ± 12.3 (n = 35)	–138.7 ± 121.5 (n = 99)
Intravitreal Treatment During the Study				
DEX only	9.4 ± 11.7 (n = 92)	7.3 ± 12.7 (n = 51)	7.9 ± 14.0 (n = 31)	–134.7 ± 122.8 (n = 74)
DEX and other treatment	8.6 ± 10.5 (n = 76)	8.0 ± 12.0 (n = 49)	5.9 ± 12.8 (n = 25)	–141.5 ± 116.4 (n = 60)
History of Vitrectomy				
Yes	12.5 ± 13.3 (n = 48)	12.6 ± 13.7 (n = 27)	13.1 ± 14.7 (n = 11)	–159.0 ± 132.5 (n = 37)
No	7.7 ± (9.9) (n = 120)	5.8 ± 11.3 (n = 73)	5.5 ± 12.8 (n = 45)	–129.6 ± 113.9 (n = 97)

SD = standard deviation; BCVA = best-corrected visual acuity; CRT = central retinal thickness; DME = diabetic macular edema; DEX = dexamethasone intravitreal implant

ser photocoagulation, and 29.4% had undergone vitrectomy. Table 2 lists baseline characteristics of the study eyes. DME had persisted for 1 year or longer in 65.6% of the study eyes. Two-thirds of the study eyes with documented lens status were pseudophakic. At baseline before DEX treatment, the mean BCVA in the study eyes was 54.4 letters (approximately 20/80 Snellen), and the mean CRT was 424.6 µm.

The study was completed by 172 (97.2%) patients. Of the five patients who exited the study early, two (1.1%) died before the study was completed, two (1.1%) were lost to follow-up, and one (0.6%) moved away from the area. Although the study protocol called for data to be collected through month 12 (360 ± 15 days) after the initial DEX injection, some physicians continued to collect and report data for a longer period of time (up to 16 months). All available data were used in the analysis.

Treatment Patterns

The mean (± standard deviation [SD]) number of DEX injections administered to study eyes was 2.0 ± 1.1 (range: one to five injections). During the study period, 77 study eyes (42.8%) received a single DEX injection, whereas 45 (25.0%), 35 (19.4%), 20 (11.1%), and three (1.7%) study eyes received two, three, four, and five DEX injections, respectively. The mean (± SD) interval between successive DEX injections was 21.8 ± 9.2 weeks (range: 7 weeks to 51 weeks). Effectiveness results are presented for the first three DEX injections, because the number of patients who received a fourth or fifth injection was too small for meaningful analysis.

In 99 study eyes (55.0%), DEX was the only treatment administered by intravitreal injection during the study. Eighty-one study eyes (45.0%) received other intravitreal injections in addition to DEX injections, most commonly intravitreal injections of aflibercept (Eylea; Regeneron, Tarrytown, NY) (21.1%), ranibizumab (Lucentis; Genentech, South San Francisco, CA) (13.9%), and bevacizumab (Avastin; Genentech, South San Francisco, CA) (9.4%). The mean number of non-DEX intravitreal injections administered during the study in these 81 study eyes was 2.8 (range: one to nine injections). Twelve study eyes (6.7%) were treated with a corticosteroid other than DEX (intravitreal triamcinolone acetonide or fluocinolone acetonide intravitreal implant) and nine study eyes

TABLE 4

Adverse Events Reported in Three or More Patients

Adverse Event, n (%)	Patient Population (n = 177)
Any adverse event	69 (39.0)
IOP increased	11 (6.2)
Conjunctival hemorrhage	8 (4.5)
Vitreous floaters	7 (4.0)
Dry eye	6 (3.4)
Ocular hypertension	6 (3.4)
Posterior capsule opacification	6 (3.4)
Glaucoma	5 (2.8)
Macular fibrosis	4 (2.3)
Vision blurred	4 (2.3)
Cataract	3 (1.7)
Eye pain	3 (1.7)
Photopsia	3 (1.7)
Vitreous detachment	3 (1.7)
Vitreous hemorrhage	3 (1.7)

IOP = intraocular pressure

(5.0%) received adjunctive retinal focal laser treatment during the study.

Visual Outcomes

Mean changes in BCVA from baseline during the study are shown in Figure 1. After the first three DEX injections, mean maximum improvement in BCVA from baseline in study eyes ranged from +7.0 approximate ETDRS letters to +9.1 letters and was statistically significant ($P < .001$). Across all DEX injections, the mean (± SD) maximum BCVA change from baseline was +11.7 letters ± 11.55 letters (95% CI, 9.97-13.46; $P < .001$, n = 172). The mean (± SD) average change in BCVA from baseline across all study visits in the AUC analysis was +3.6 letters ± 9.0 letters (95% CI, 2.27-4.97).

Among the 172 study eyes with baseline BCVA data, 99 (57.6%) and 62 (36.0%) achieved an improvement in BCVA from baseline of 10 or more and 15 or more approximate ETDRS letters, respectively. The time to initial gain of 10 or more and 15 or more letters was typically 2 to 3 months for study eyes that achieved this magnitude of BCVA improvement (Figure 2A). The time to improvement in BCVA to 20/40 or better also was typically 2 to 3 months (Figure 2B). BCVA improved to 20/40 or better in 50 (42.7%) of the 117 study eyes with baseline BCVA worse than 20/40.

Subgroup Analysis

DEX treatment was associated with beneficial effects on BCVA and CRT in subgroups defined by baseline lens status, duration of DME, prior laser treatment for DME, prior vitrectomy, and pattern of DEX use during the study (Table 3). The mean (SD) maximum change in BCVA from baseline across all DEX injections was 12.2 (13.5) letters in baseline phakic eyes versus 11.5 (11.2) letters in baseline pseudophakic eyes. In eyes that received intravitreal injections of DEX only, the mean (SD) maximum change in BCVA from baseline across all DEX injections was 11.5 (11.7), compared with 11.8 (11.5) in eyes that received DEX and other intravitreal injections.

Anatomic Outcomes

For the 134 study eyes with both baseline and post-baseline CRT data, the mean (SD) maximum change in CRT during the study was −137.7 (119.6) µm (95% CI, −158.15 to −117.29; $P < .001$). Mean change in CRT from baseline ranged from −121.2 µm to −140.3 µm after the first three DEX injections and was statistically significant at all months through month 12 ($P \leq .012$) (Figure 3). CRT improved to 300 µm or less in 50 (45.0%) of the 111 study eyes with baseline CRT greater than 300 µm. Among the 98 study eyes with baseline BCVA worse than 20/40 and baseline CRT greater than 300 µm, 19 (19.4%) achieved both BCVA

of 20/40 or better and CRT of 300 µm or less at the same visit during the study.

Safety Findings

AEs were reported in 69 of 177 patients (39.0%) treated with DEX in this study. The most common AEs were ocular and included increased IOP, conjunctival hemorrhage, vitreous floaters, dry eye, ocular hypertension, and posterior capsule opacification (Table 4). Fourteen serious AEs occurred in 10 patients; the only serious AEs considered by the investigator to be related to DEX injection were endophthalmitis in two patients (1.1%). Two (1.1%) patients died during the study for reasons considered by the investigator to be unrelated to DEX (a cardiac disorder and a diabetic complication).

A similar increase in mean IOP was seen after each of the first three DEX injections (Figure 4). Among all 180 study eyes, 22 (12.2%) had an IOP measurement of 25 mm Hg or greater, five (2.8%) had an IOP measurement of 35 mm Hg or greater, and 23 (12.8%) had an increase in IOP from baseline of 10 mm Hg or greater during the study. One or more IOP-lowering medications were used in 22.8% of study eyes (41 of 180). One study eye that had a prior history of trabeculoplasty underwent a repeat trabeculoplasty during the study. No glaucoma incisional surgeries during the study were reported.

Fifteen (8.3%) study eyes underwent cataract surgery during the study. Other common ocular surgeries and procedures were pars plana vitrectomy in eight (4.4%) study eyes and panretinal photocoagulation in eight (4.4%) study eyes.

DISCUSSION

The treatment of DME has evolved during the past decade, with a progressive reduction in the use of focal laser therapy and a concomitant increase in utilization of intravitreal injections. The accompanying improvements in visual and anatomic outcomes have come at the cost of an increased frequency of annual clinic visits, with one center reporting a tripling in the number of patient visits from three to nine per year.[12] Compared with anti-VEGF inhibitors, which currently dominate the treatment landscape, the use of sustained-release corticosteroids has the potential to reduce the injection burden for patients with DME while also offering therapeutic benefit.[7] In addition, the durable action of intravitreal corticosteroids facilitates combination therapy.

The present study was conducted to better understand the usage and outcomes of DEX treatment in DME patients in a clinical practice setting. Treatment with DEX 0.7 mg alone or in combination with other DME therapy was effective in improving both visual and anatomic outcomes in this real-world population of patients, who typically had chronic, treatment-refractory DME. BCVA improved by a mean of +9.1, +7.7, and +7.0 approximate ETDRS letters after the first, second, and third DEX injection, respectively. The mean peak improvement in CRT was –137.7 µm, and 45% of patients with baseline CRT of greater than 300 µm achieved CRT of 300 µm or less during the study. DEX injections were administered on average at 5-month intervals. No new safety concerns were identified, and DEX injections were well tolerated.

The present study was not the first real-world study to assess DEX in patients with DME. Previously, the CHROME study evaluated DEX 0.7 mg in 120 study eyes with macular edema, including 34 eyes with DME, during a period of 6 months.[13] In the subpopulation of patients with DME, the mean peak improvement in CRT was consistent with the present findings at –190.9 µm, and the mean peak improvement in BCVA in pseudophakic study eyes (1.5 Snellen lines equivalent, n = 23) was also consistent with the present findings. In the CHROME study, there was no significant improvement in the 11 phakic study eyes with DME. Possible reasons contributing to the lack of BCVA improvement seen in phakic study eyes might include the small sample size, the presence of long-standing DME with associated photoreceptor damage, or cataract development. Another real-world study conducted in Korea found that in patients with DME, DEX improved mean BCVA from 0.60 logMAR at baseline to 0.49 logMAR at 3 months and 0.55 logMAR at 6 months (mean improvement of 6 and 3 approximate ETDRS letters, respectively), and the mean CRT improved from 491.6 µm at baseline to 357.7 µm at 3 months and 412.5 µm at 6 months.[14] Consistent with the present study, 48.9% of patients received additional treatment with intravitreal anti-VEGF therapy or a second DEX injection within 6 months, and the mean treatment-free interval was 4.4 months after the first DEX injection. Finally, in a real-world study of the dosing regimens of DEX used for DME treatment in France, the mean DEX injection interval was 4.9 months, with an average of 2.4 injections administered per year for patients with DME.[15]

Cataract progression and increases in IOP are side effects associated with intravitreal corticosteroids, and when they occur, prompt treatment is required for optimal outcomes.[10] No cataract or glaucoma surgeries were required in a previously reported retrospective real-world study of 78 patients with DME who were treated with DEX, but in that study, patients received a single DEX treatment, and the follow-up was only 6 months.[16] In the present study, cataract was reported

as an AE in three patients (1.7%), and 15 study eyes (8.3%) underwent cataract surgery. Glaucoma was reported as an AE in five patients (2.8%). IOP increased to 25 mm Hg or higher in 12.2% of study eyes, but there was no evidence for a cumulative effect of sequential implants on IOP, and increases in IOP were generally managed with topical IOP-lowering medication. No patient required glaucoma incisional surgery. In the 3-year MEAD study, a similar percentage of DME patients with and without an IOP increase of 10 mm Hg or more achieved a 15-letter or greater BCVA improvement with DEX 0.7 mg, suggesting that the benefits of DEX treatment are not affected by IOP increases, which are typically well-managed with topical IOP-lowering medications.[17]

One limitation of this study, common to observational studies, is that there was no standardization of the type and timing of assessments, and many patients had missing data. For example, baseline BCVA data were missing for 4.4% of study eyes (eight of 180), and only 74% of study eyes (134 of 180) had any change from baseline CRT data available. Secondly, although data were collected for 12 months for most patients, the period of follow-up was variable, and some patients had data collected and analyzed beyond 12 months. Finally, use of treatments in addition to DEX implant was allowed and could have influenced the efficacy and safety outcomes. However, the majority of patients (55%) received no intravitreal therapy other than DEX implant during the study period, and improvements in BCVA and CRT were observed in the subgroup of patients treated with intravitreal DEX implant only, as well as in the subgroup of patients who received other intravitreal therapy.

In conclusion, the findings of this prospective, multicenter, observational study show that treatment of DME with DEX, either as monotherapy or in combination with other modalities of DME therapy, improves BCVA and CRT in real-world clinical practice. DEX injection frequency was consistent with previous reports, and no new safety concerns were identified.

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