EFFICACY AND SAFETY OF TWO OR MORE DEXAMETHASONE INTRAVITREAL IMPLANT INJECTIONS FOR TREATMENT OF MACULAR EDEMA RELATED TO RETINAL VEIN OCCLUSION (SHASTA STUDY)

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Purpose: To evaluate the efficacy, safety, and reinjection interval of dexamethasone intravitreal implant (DEX implant) in branch retinal vein occlusion and central retinal vein occlusion patients receiving ≥2 DEX implant treatments.

Methods: Multicenter (26-site), retrospective chart review study. Data were collected from baseline (at first DEX implant) through 3 months to 6 months after last DEX implant.

Results: Patients (n = 289) received 2 to 9 (mean, 3.2) DEX implants as monotherapy (29.1% of patients) or with adjunctive treatments/procedures. Mean duration of macular edema before first DEX implant was 18.4 months. Mean reinjection interval was 5.6 months. Mean peak change in best-corrected visual acuity from baseline through 4 weeks to 20 weeks after final DEX implant was +1.0 line ($P < 0.001$). Best-corrected visual acuity and central retinal thickness improved significantly from baseline after each of the first 6 DEX implant injections ($P \leq 0.037$); 59.7% of branch retinal vein occlusion and 66.7% of central retinal vein occlusion patients achieved ≥2-line best-corrected visual acuity improvement. Intraocular pressure increase (≥10 mmHg) occurred in 32.6% of patients; 29.1% used intraocular pressure-lowering medication to treat increases associated with DEX implant. Only 1.7% of patients required incisional glaucoma surgery.

Conclusion: Retinal vein occlusion patients treated with multiple DEX implant injections, either alone or combined with other therapies, had improved central retinal thickness and visual acuity with each subsequent injection. No new safety concerns developed with multiple implants.

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Retinal vein occlusion (RVO) is a common retinal vascular disease associated with vision loss.[1] Central retinal vein occlusion (CRVO) has a lower prevalence than branch retinal vein occlusion (BRVO) but is often associated with worse visual outcomes.[1] Macular edema is a frequent complication and cause of vision loss in both BRVO[2] and CRVO.[3] Early initiation of treatment for macular edema secondary to RVO results in better visual outcomes and limits irreparable retinal damage.[4,5]

Until recently, laser photocoagulation has been standard care for macular edema in BRVO, where it has been shown to improve visual acuity.[6] Observation has been standard care for macular edema in CRVO, as laser photocoagulation decreases macular edema in CRVO but typically does not improve visual acuity.[7,8] Options for treatment of macular edema associated with RVO have expanded in the past few years, as intravitreal corticosteroid treatment[9–11] and intravitreal treatment targeted against vascular endothelial growth factor (VEGF)[12–14] have been shown to effectively reduce macular edema and help improve visual acuity after BRVO and CRVO. Phase 3 clinical trials typically evaluate the therapeutic efficacy of a single pharmacologic

agent. In practice, multiple intravitreal treatments with corticosteroids and/or anti-VEGF agents may be required for optimal outcomes in macular edema secondary to RVO. The algorithms, timing, and number of treatments used by physicians in the context of routine patient care are not yet well defined.

Sustained-release dexamethasone intravitreal implant (DEX implant; Ozurdex; Allergan, Inc, Irvine, CA) is composed of a biodegradable copolymer of polylactic-co-glycolic acid containing micronized dexamethasone.[10] Dexamethasone is slowly released from the implant over several months as the copolymer matrix degrades to lactic acid and glycolic acid, which are metabolized to water and carbon dioxide.[15] In an early study, DEX implant treatment of persistent macular edema attributable to various causes, including RVO, provided significant improvements in best-corrected visual acuity (BCVA), macular thickness, and fluorescein leakage compared with observation.[16] Subsequently, 2 identical, randomized, sham-controlled 6-month clinical trials demonstrated that a single treatment with DEX implant 0.7 mg was well tolerated and significantly improved BCVA and anatomical outcomes compared with sham treatment in patients with BRVO and CRVO.[10] In an open-label extension of the 6-month study, safety and efficacy results were similar after a second DEX implant injection, although an increase in cataract progression was noted.[11]

Dexamethasone intravitreal implant 0.7 mg was approved by the United States Food and Drug Administration in June 2009 for the treatment of macular edema after BRVO and CRVO. This retrospective chart review study examined the subsequent use of DEX implant 0.7 mg in clinical practice in the United States in a "real-world" setting. In the Phase 3 clinical studies, patients were given 1 or 2 DEX implant treatments.[11] The purpose of the present study was to report the efficacy, safety, and reinjection interval of DEX implant 0.7 mg in the treatment of macular edema secondary to RVO in patients receiving 2 or more DEX implant treatments in the course of routine clinical care.

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Methods

In this retrospective, multicenter, open-label Phase 4 clinical study, patients who were treated with multiple injections of DEX implant for macular edema secondary to RVO at 26 sites in the United States were identified by review of patient charts from June 2009 through February 2012. The study was conducted in compliance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Health Insurance Portability and Accountability Act. Institutional review board/ethics committee approval was obtained at each investigational site, and all patients provided written informed consent. The study is registered with the identifier NCT01411696 at ClinicalTrials.gov.

The study included patients at least 18 years of age diagnosed with macular edema secondary to RVO in the study eye, who had received at least 2 intravitreal injections of DEX implant 0.7 mg in the study eye and who had follow-up data available at a minimum of 3 months after the latest DEX implant injection. The key patient exclusion criterion was previous treatment with DEX implant as part of or during a clinical study. Procedures and intravitreal injections, in addition to DEX implant injections, for treatment of RVO-associated macular edema were allowed. If both eyes of a patient met the study eligibility criteria, the eye with the greatest number of DEX implant injections was designated as the study eye.

Dexamethasone intravitreal implant 0.7 mg was placed in the vitreous with a single-use applicator system in an office procedure.[17] Efficacy and safety data were collected from patient charts for all visits from the time of the first DEX implant injection (baseline visit) through a minimum of 3 months and up to a maximum of 6 months after the last DEX implant injection. These data included Snellen BCVA, optical coherence tomography, fluorescein angiography, intraocular pressure (IOP), concomitant IOP-lowering medications, biomicroscopy, ophthalmoscopy, cataract or glaucoma surgeries, DEX implant injections, other intravitreal injections or procedures for treatment of RVO-associated macular edema, and adverse events. The assessments of BCVA and other parameters were not standardized. Demographic data and medical and ophthalmic history were obtained from records of the baseline visit.

The primary efficacy endpoint was the mean change in BCVA (number of lines) from baseline at 4 weeks to 20 weeks after the last DEX implant injection. If more than one assessment of BCVA was made during that period, the BCVA demonstrating the greatest

improvement from baseline (peak effect) was used in the analysis. Key secondary efficacy endpoints included the percentage of patients with at least 2-line improvement in BCVA from baseline, the percentage of patients with at least 3-line improvement in BCVA from baseline, and the change in central retinal thickness from baseline by optical coherence tomography. For the latter analysis, baseline central retinal thickness was defined as the last value measured on or before the day of the first DEX implant injection. Key safety measures included adverse events and IOP.

All data analyses were based on observed values with no imputation of missing values. The method described by Gregori et al[18] was used to convert Snellen visual acuity measurements to approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores for analysis. Changes in BCVA and central retinal thickness from baseline were evaluated with paired *t*-tests. Peak effect was defined as the maximum BCVA or the minimum optical coherence tomography value for central retinal thickness.

Post hoc subgroup analyses of key baseline, efficacy, and safety parameters for BRVO and CRVO patients were conducted to evaluate any differences based on disease entity. Additional analyses included tabulation and summary of the number of injections. SAS version 9.2 (SAS Institute Inc, Cary, NC) and a 2-sided alpha level of 0.05 were used for the statistical analyses.

Results

Study Population

A total of 289 patients satisfied the eligibility criteria for study entry. Of these, 157 (54.3%) were diagnosed with BRVO and 132 (45.7%) were diagnosed with CRVO. The demographics and baseline characteristics of the subgroups of patients with BRVO and CRVO were similar and are listed in Table 1. Overall, the mean age of the patients was 71.9 years, and over half (57.4%) were women. Race and ethnicity information was recorded on about half of the charts; most of the patients with data available were white and non-Hispanic. Almost one third of the patients (31.5%) had glaucoma or ocular hypertension at baseline, and 15.6% had a history of IOP elevation in response to steroid treatment documented in their charts at baseline. Thirty-seven patients (12.8%) had a history of pars plana vitrectomy at baseline.

The macular edema associated with RVO diagnosis had a mean duration of 18.4 months (median duration of 8.2 months, range from 0 to 150.2 months) at baseline. The mean time between diagnosis of RVO-related macular edema and the first DEX implant treatment was 20.1 months in BRVO patients and 16.4 months in CRVO patients (Table 1). Ischemia was reported in 30.4% of the study eyes at baseline. Most of the patients (85.8%) had been treated previously; only 13.5% were treatment naive and had not received intravitreal or laser treatment for RVO-associated complications before the first DEX implant injection. The previous treatments received by patients are listed in Table 2. Among all patients, 38.8% had undergone focal and/or panretinal laser photocoagulation, 70.9% had received intravitreal anti-VEGF treatment, and 39.8% had received intravitreal triamcinolone treatment before beginning DEX implant treatment.

Dexamethasone Intravitreal Implant Treatment

The mean (SD) period for data collection (from the time of the first DEX implant injection to up to 6 months after the last DEX implant injection) was 1.2 (0.5) years. Patients were administered at least 2 and up to 9 intravitreal injections of DEX implant during this period. The mean (SD) number of DEX implant treatments given to patients was 3.2 (1.5) for the total patient population, 3.2 (1.4) for the BRVO subgroup, and 3.2 (1.5) for the CRVO subgroup. Most patients received two to four DEX implant injections. As only 10 patients received 7 or more DEX implant injections, data for 7, 8, and 9 injections are reported as text on Figures 1 and 2. Based on the mean number of days between DEX implant injections for each patient, the mean reinjection interval between DEX implant treatments was 5.6 months, and the median time between DEX implant treatments was 4.9 months (Table 3). Overall, 68.5% of patients had a mean interval between DEX implant injections of 4 months to 6 months.

Efficacy

The mean (SD) peak change in BCVA from baseline at 4 weeks to 20 weeks after the final DEX implant injection was an improvement of 1.0 (3.5) line (equivalent to 5 ETDRS letters; primary efficacy endpoint, $P < 0.001$). Mean (SD) peak changes in BCVA from baseline at 4 weeks to 20 weeks after the first, second, third, fourth, fifth, and sixth DEX implant injection (and before the next injection) were also statistically significant ($P \leq 0.037$) and corresponded to improvements of 1.6 (2.9), 1.2 (3.4), 1.4 (3.2), 1.2 (3.2), 1.1 (3.2), and 2.9 (3.2) lines, respectively.

Figure 1 shows the percentage of patients with at least 2- or 3-line improvement in BCVA from baseline

Table 1. Baseline Demographics and Patient Characteristics

	All Patients (n = 289)	BRVO Patients (n = 157)	CRVO Patients (n = 132)
Age, years			
Mean (SD)	71.9 (11.0)	72.2 (11.2)	71.6 (10.7)
Range	39–94	39–94	39–91
Sex, n (%)			
Female	166 (57.4)	92 (58.6)	74 (56.1)
Male	123 (42.6)	65 (41.4)	58 (43.9)
Race, n (%)			
White	142 (49.1)	67 (42.7)	75 (56.8)
Black or African American	9 (3.1)	6 (3.8)	3 (2.3)
Asian	7 (2.4)	6 (3.8)	1 (0.8)
Pacific Islander	1 (0.3)	0 (0.0)	1 (0.8)
Not recorded	130 (45.0)	78 (49.7)	52 (39.4)
Ethnicity, n (%)			
Hispanic or Latino	10 (3.5)	8 (5.1)	2 (1.5)
Not Hispanic or Latino	137 (47.4)	65 (41.4)	72 (54.5)
Not recorded	142 (49.1)	84 (53.5)	58 (43.9)
Diagnosis in study eye, n (%)			
BRVO	157 (54.3)	157 (100.0)	NA
CRVO	132 (45.7)	NA	132 (100.0)
Ischemia in study eye, n (%)			
Yes	88 (30.4)	55 (35.0)	33 (25.0)
No	193 (66.8)	97 (61.8)	96 (72.7)
Unknown	6 (2.1)	4 (2.5)	2 (1.5)
Not recorded	2 (0.7)	1 (0.6)	1 (0.8)
Lens status in study eye, n (%)			
Phakic	128 (44.3)	69 (43.9)	59 (44.7)
Pseudophakic	158 (54.7)	86 (54.8)	72 (54.5)
Not recorded	3 (1.0)	2 (1.3)	1 (0.8)
Comorbid glaucoma or ocular hypertension, n (%)			
Yes	91 (31.5)	44 (28.0)	47 (35.6)
Using IOP-lowering medication at baseline	70 (24.2)	35 (22.3)	35 (26.5)
No or not recorded in chart	198 (68.5)	113 (72.0)	85 (64.4)
History of IOP response to steroid, n (%)			
Yes	45 (15.6)	22 (14.0)	23 (17.4)
No	168 (58.1)	92 (58.6)	76 (57.6)
Not recorded	76 (26.3)	43 (27.4)	33 (25.0)
Duration of RVO at time of first DEX implant injection (months)			
Mean (SD)	18.4 (23.4)	20.1 (25.0)	16.4 (21.3)
Range	0.0–150.2	0.0–119.1	0.0–150.2
Mean (SD) BCVA in the study eye (lines)	9.8 (4.6)	11.0 (4.3)	8.4 (4.7)
Snellen	20/100	20/80	20/160
Mean (SD) central retinal thickness, μm	438 (182)	413 (149)	469 (201)

NA, not applicable.

after intravitreal injection of DEX implant. The percentage of patients responding to treatment with at least 2- or 3-line improvement in BCVA from baseline was similar after each DEX implant injection. After the first to sixth DEX implant injections, at least 2-line improvement in BCVA from baseline was seen in 38.5% to 55.6% of patients, and at least 3-line improvement in BCVA from baseline was seen in 30.4% to 50.0% of patients. Overall, 62.9% of patients demonstrated at least 2-line improvement in BCVA from baseline and 48.1% of patients demonstrated at least 3-line improvement in BCVA from baseline at some point after DEX implant treatment. Subgroup analysis showed similar results for BRVO and CRVO patients, with at least 2-line improvement in BCVA from baseline seen in 59.7% of BRVO patients and 66.7% of CRVO patients during the study period. After the first through sixth DEX implant injections, 46.8% to 55.6% of BRVO patients and 26.3% to 55.6% of CRVO patients had at least 2-line improvement in BCVA from baseline, whereas 27.9% to 44.4% of BRVO patients and 20.6% to 55.6% of CRVO patients had at least 3-line improvement in BCVA from baseline.

Table 2. Intraocular Treatments and Procedures for Complications of RVO in the Study Eye Before and After the First DEX Implant Injection*

Treatment or Procedure	Before the First DEX Implant Injection† (n = 289)	After the First DEX Implant Injection (n = 289)
Any treatment or procedure for RVO (other than DEX implant), n (%)	248 (85.8)	205 (70.9)
Intravitreal injection, n (%)		
Anti-VEGF treatment	205 (70.9)	186 (64.4)
Intravitreal bevacizumab	181 (62.6)	127 (43.9)
Intravitreal ranibizumab	40 (13.8)	94 (32.5)
Intravitreal pegaptanib	3 (1.0)	0 (0.0)
Intravitreal triamcinolone	115 (39.8)	9 (3.1)
DEX implant	0 (0.0)	289 (100.0)
Laser/surgical intervention, n (%)		
Any laser treatment	112 (38.8)	72 (24.9)
Focal laser	85 (29.4)	54 (18.7)
Panretinal photocoagulation	45 (15.6)	27 (9.3)
Pars plana vitrectomy	37 (12.8)	3 (1.0)
No treatment or procedure for RVO (other than DEX implant), n (%)	39 (13.5)	84 (29.1)
No record	2 (0.7)	0 (0.0)

*Patients could receive more than one type of treatment or procedure before and after DEX implant treatment.
†Medical and surgical histories for particular treatments and procedures were not recorded in up to 25 (8.7%) of the patient charts.

The mean (SD) baseline central retinal thickness for all patients with baseline data available (n = 247) was 438 (182) μm. The mean central retinal thickness improved from baseline after the first DEX implant injection ($P < 0.001$) and was similarly improved from baseline after the second, third, fourth, fifth, and sixth DEX implant injections ($P \leq 0.002$, Figure 2). Mean changes in central retinal thickness from baseline ranged from −154 μm to −188 μm after the first 6 DEX implant injections. Among all patients with postbaseline central retinal thickness measurements, the percentage who achieved central retinal thickness of ≤250 μm at any time point after DEX implant treatment was 65.3% (188/288). The percentage of patients who achieved central retinal thickness of ≤250 μm after DEX implant injection was similar for BRVO patients (66.0% [103/156]) and CRVO patients (64.4% [85/132]).

Overall, use of intravitreal anti-VEGF agents, intravitreal triamcinolone, and laser photocoagulation treatments for RVO-associated macular edema was reduced after the initiation of DEX implant treatment (Table 2). Laser procedures for treatment of complications of RVO were performed in 38.8% of patients before DEX implant treatment and 24.9% of patients after the first DEX implant injection. The percentage of patients who were given anti-VEGF treatment was also reduced, from 70.9% before DEX implant treatment to 64.4% after the first DEX implant injection. The mean (SD) number of anti-VEGF injections received by patients was 3.4 (4.7) before DEX implant treatment and 1.9 (2.2) after the first DEX implant injection. Among the 186 patients who were treated with intravitreal anti-VEGF therapy after beginning DEX implant treatment, the mean (SD) interval between the first DEX implant injection and the next anti-VEGF injection was 180 (125) days. The interval was >90 days for 81.2% of the patients and >180 days for 39.8% of the patients (Table 4).

Safety

Treatment-related adverse events were reported for 24.6% (71/289) of the patients. There were no deaths and no serious adverse events related to treatment. Increases in IOP and cataract progression were the only treatment-related adverse events with an incidence of 2% or higher.

Among all patients, 32.6% had an increase in IOP from baseline of at least 10 mmHg, 33.7% had IOP of 25 mmHg or higher, and 9.4% had IOP of 35 mmHg or higher at 1 or more visits during the study period (Table 5). Increases in IOP were more likely in patients with a history of IOP response to steroid treatment. For example, postbaseline IOP of 25 mmHg or higher was reported in 44.4% (20/45) of patients with a history of IOP response to steroid treatment versus 31.1% (52/167) of patients with no such history. During the study period, 139 patients (48.1%) used IOP-lowering medication, including 70 patients (24.2%) with glaucoma or ocular hypertension who were using IOP-lowering medication at baseline before the first DEX implant, and 69 patients (23.9%) who first began use of IOP-lowering medication during the study.

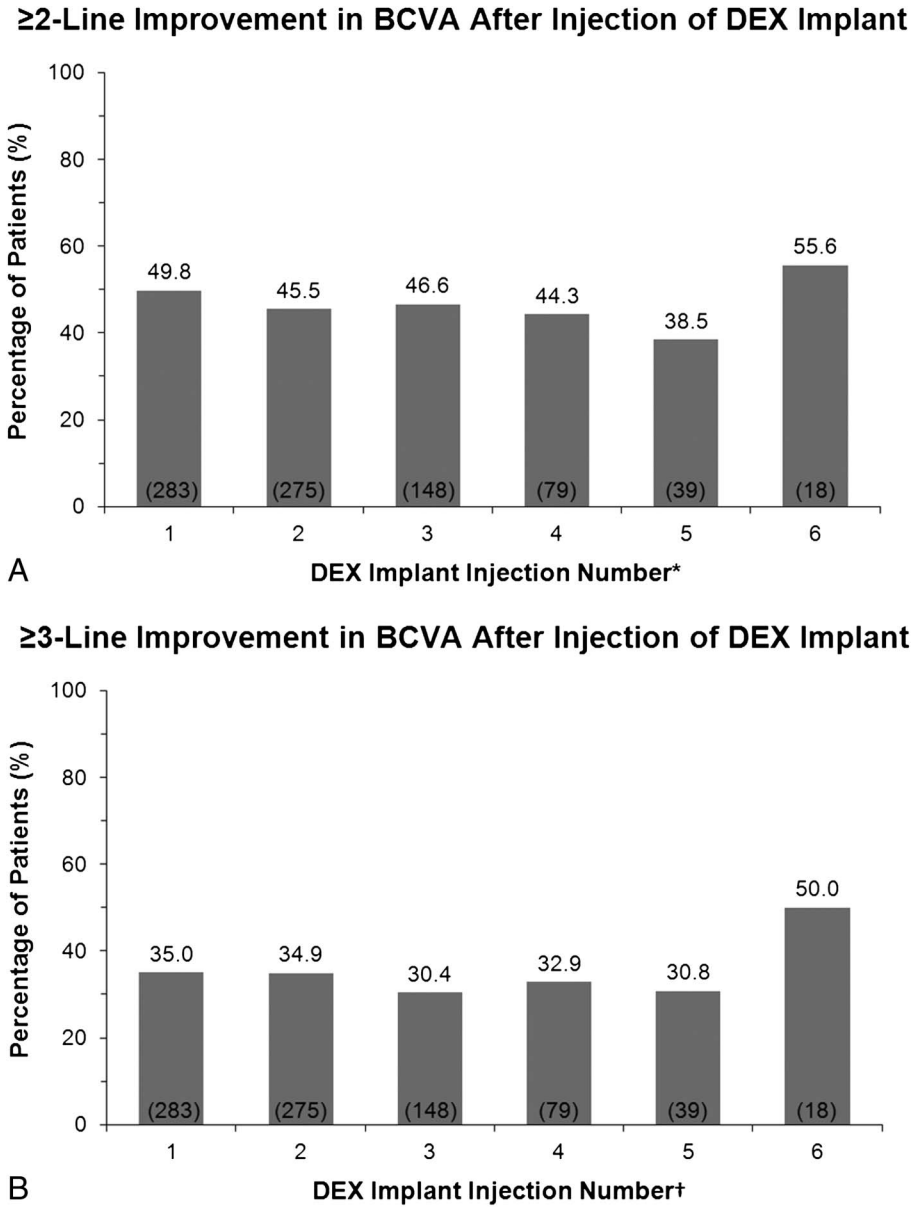

Fig. 1. Percentage of patients with at least (**A**) 2-line or (**B**) 3-line improvement in BCVA from baseline after each intravitreal injection of DEX implant. The results shown are based on the peak improvement in BCVA seen after the indicated DEX implant injection and before the next DEX implant injection. The number (n) for each injection is shown in parentheses. *Injection 7: 83.3% (5/6 patients); injection 8: 100.0% (3/3 patients); injection 9: 100.0% (1/1 patient). †Injection 7: 83.3% (5/6 patients); injection 8: 66.7% (2/3 patients); injection 9: 100.0% (1/1 patient).

Dexamethasone intravitreal implant treatment was considered by the investigator to be the reason for use of an IOP-lowering medication in 84 patients (29.1%), including 33 patients (11.4%) who were using IOP-lowering medication at baseline but required a change in therapy, and 51 patients (17.6%) who initiated IOP-lowering medication during the study. Four patients (1.4%) underwent glaucoma laser surgery and 5 (1.7%) underwent glaucoma incisional surgery during the study period (Table 5). Seven of these patients had been diagnosed with glaucoma or ocular hypertension and were using IOP-lowering medication before beginning DEX implant treatment. The mean (SD) change in IOP from baseline at the final visit (3–6 months after the last DEX implant injection) was 0.7 (5.35) mmHg overall, 0.0 (4.9) mmHg in BRVO patients, and 1.4 (5.8) mmHg in CRVO patients. At the final visit, most patients (91.5% [260/284]) had IOP of 21 mmHg or lower, although 14 patients (4.9%) had IOP of 25 mmHg or higher and 5 patients (1.8%) had IOP of 35 mmHg or higher (Table 5).

Forty-six patients underwent cataract surgery during the study period. The mean (SD) age of these patients was 67.2 (8.7) years. Of these patients, 85% (39/46) had lens opacity at baseline; the baseline opacity was Grade 2 in 22 patients (48%) and Grade 3 in 6 patients (13%).

Table 3. Time Between DEX Implant Injections*

Mean Interval Between DEX Implant Injections for Each Patient	No. Patients (%)
1 Month (≤45 days)	0 (0.0)
2 Months (46–75 days)	0 (0.0)
3 Months (76–105 days)	25 (8.7)
4 Months (106–135 days)	86 (29.8)
5 Months (136–165 days)	73 (25.3)
6 Months (166–195 days)	39 (13.5)
>6 Months (>195 days)	66 (22.8)
Mean (SD) across all patients, days	169 (74)
Months	5.6
Median, days	150
Months	4.9
Range, days	81–527

*Based on the mean number of days between injections for each patient.

Discussion

In this retrospective case series, treatment of eyes with macular edema secondary to RVO with two or more injections of DEX implant had favorable visual and anatomical outcomes. Eyes treated with DEX implant had a mean improvement in BCVA from baseline of 1 line (equivalent to 5 EDTRS letters) at the last examination from 3 months to 6 months after the final DEX implant injection ($P < 0.001$). The effect of repeated DEX implant treatments on BCVA was consistent and demonstrated durability over repeat injections. After each of the first 6 injections of DEX implant, ~46% of eyes had at least 2 lines and ~34% had at least 3 lines of improvement in BCVA from baseline. Each treatment with DEX implant also produced similar significant mean reductions in central retinal thickness measured by optical coherence tomography. The anatomical improvements in central retinal thickness in individual patients were not always associated with improvements in BCVA, perhaps because of ischemia and irreversible tissue damage caused by a long duration of edema before DEX implant treatment. These results are consistent with previous reports of only a modest correlation between visual and anatomical outcomes after the treatment of persistent macular edema associated with RVO and other conditions.[19]

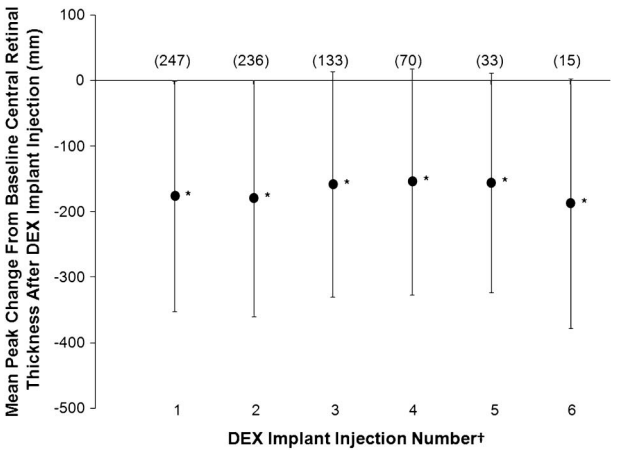

Fig. 2. Mean change in central retinal thickness from baseline after each intravitreal injection of DEX implant. Central retinal thickness was evaluated by optical coherence tomography. The results shown are based on the peak change in central retinal thickness seen after the indicated DEX implant injection and before the next DEX implant injection. The number (n) for each injection is shown in parentheses. Error bars, SD. *$P \leq 0.002$. †Injection 7: −255 μm (n = 4); injection 8: −75 μm (n = 1); injection 9: −61 μm (n = 1).

The efficacy demonstrated by DEX implant in this real-world study was comparable with that shown in the GENEVA Phase 3 clinical studies of DEX implant for macular edema after RVO.[10,11] In the Phase 3 studies, the cumulative response rate in achieving at least 3-line improvement in BCVA during the 6 months after the initial treatment with DEX implant was 41%,[10] and similar improvements in BCVA were seen after a second injection of DEX implant in the open-label study extension.[11] Decreases in central retinal thickness were also significant and similar after the first and second DEX implant treatments in the Phase 3 studies.[11] In the present study, subgroup analysis by type of RVO (BRVO or CRVO) showed improvements in visual acuity and reduction in macular edema after each DEX implant treatment regardless of the diagnosis. Similarly in the Phase 3 studies, visual acuity improved after DEX implant treatment of macular edema associated with either BRVO or CRVO, although the mean improvement was slightly greater and the improvement was better sustained in eyes with BRVO.[10]

There were no unexpected safety findings in the study. The treatment-related adverse events recorded in patient charts were consistent with the known safety profile of DEX implant treatment. The most frequent adverse effects of treatment were increases in IOP and cataract progression. Cataract surgery was performed during the study period in 46 patients at the discretion of the patient and physician, although 28 (61%) had lens opacity recorded as Grade 2 or higher at baseline. The relationship between DEX implant treatment and the need for cataract surgery could not easily be determined from the patient charts.

Previous clinical studies have shown that when IOP increases occur after DEX implant injections, they are usually transient, moderate in severity, and readily managed with IOP-lowering medication.[10,11] In the present study, at the time of their first DEX implant treatment, almost one third of the patients (31.5%) had preexisting glaucoma or ocular hypertension,

Table 4. Time to the First Anti-VEGF Injection for Patients With Anti-VEGF Treatment Added to DEX Implant Treatment (n = 186)

Time Between the First DEX Implant Injection and Next Anti-VEGF Injection (Days)	Patients With Anti-VEGF Injection After the First DEX Implant Injection, n (%)
≤30	11 (5.9)
>30 to ≤60	12 (6.5)
>60 to ≤90	12 (6.5)
>90 to ≤120	45 (24.2)
>120 to ≤150	23 (12.4)
>150 to ≤180	9 (4.8)
>180	74 (39.8)

and 24.2% of the patients were using IOP-lowering medication. This finding was not unexpected because glaucoma and ocular hypertension are known risk factors for RVO.[1] Furthermore, 15.6% of the patients had a documented history of IOP elevation in response to steroid treatment. These patients with a history of IOP response to steroid, as well as any patients using two or more IOP-lowering medications in the study eye, would have been excluded from the Phase 3 study of DEX implant treatment in RVO.[10,11] Despite the inclusion of these patients, the rate of occurrence of increases in IOP in this study was similar to that in the Phase 3 study: 32.8% of eyes treated with 2 DEX implants had at least a 10-mmHg increase in IOP at some point in the 1-year Phase 3 study compared with 32.6% of study eyes in this study. Intraocular pressure-lowering medication was used to treat IOP increases associated with DEX implant treatment in 29.1% of patients in this study. Over 90% of the patients had controlled IOP of 21 mmHg or less at the final visit, 3 months to 6 months after the last DEX implant treatment, and only 1.7% of patients underwent glaucoma incisional surgery during the study. Most of the patients who had this surgery (4 of 5) had been diagnosed with glaucoma or ocular hypertension before their first DEX implant treatment.

The acceptable safety profile of two or more DEX implant injections in this study is consistent with recent reports of a case study[20] and a small case series[21] in which patients received multiple injections of DEX implant. Additional preliminary studies also identified few ocular safety concerns with repeat administration of DEX implants, and a low incidence of ocular hypertension and cataracts was reported after retreatment with DEX implant at average intervals of 20 weeks to 23 weeks (Kiss S, Wessel M. Multiple treatments of the sustained-release dexamethasone implant for the treatment of posterior non-infectious uveitis. *IOVS* 2012;53:E-Abstract 1185; Wessel M, D'Amico D, Kiss S. Multiple treatments of the sustained-release dexamethasone implant in retinal vein occlusion. *IOVS* 2012;53:E-Abstract 2243).

The baseline patient characteristics in this retrospective chart review may suggest a difficult-to-treat patient population because of the duration of edema and the number of previous RVO treatments. Almost all of the patients had been treated previously for complications of RVO. Recent reports suggest that patients with macular edema associated with BRVO[12,22,23] and CRVO[4,13] respond better to early treatment initiated soon after the emergence of symptoms, yet patients in this study had RVO of long duration; the mean interval from the diagnosis of RVO to the first DEX implant injection was 18.4 months. In addition, ischemia at baseline was recorded for ~30% of the patients, and the mean baseline BCVA in the patients with CRVO was only 20/160. Both ischemia and poor visual acuity at baseline are known to lead to worse visual outcomes in treating RVO.[2,24]

The use of other intravitreal therapies and procedures for macular edema was reduced after beginning DEX implant treatment, and approximately one third of

Table 5. Safety Assessments Related to Increases in IOP

IOP Safety Parameter	Proportion (%) of Patients
Glaucoma surgery during study period	9/289 (3.1)
Glaucoma laser surgery	4/289 (1.4)
Glaucoma incisional surgery	5/289 (1.7)
Use of IOP-lowering medication during study period because of DEX implant treatment	84/289 (29.1)
IOP elevated at any point in the study period	
≥10 mmHg increase from baseline at any visit	91/279 (32.6)
≥25 mmHg at any visit	97/288 (33.7)
≥35 mmHg at any visit	27/288 (9.4)
IOP elevated at final study visit	
≥10 mmHg increase from baseline at final visit	12/276 (4.3)
≥25 mmHg at final visit	14/284 (4.9)
≥35 mmHg at final visit	5/284 (1.8)

patients (29.1%) received only DEX implant monotherapy. Although two thirds of the patients (64.4%) received 1 or more injections of anti-VEGF therapy during the study period, the mean number of anti-VEGF injections decreased from 3.4 to 1.9 after beginning DEX implant treatment. The mean time to the first anti-VEGF treatment after the initial DEX implant injection was ~6 months. These results indicate that in most cases, DEX implant treatment was used concomitantly with other treatments in this study population with chronic, difficult-to-treat RVO-related macular edema. Consistent with the results of this study, sequential treatment with anti-VEGF bevacizumab and DEX implant was recently shown to be effective in improving visual acuity and macular thickness in a prospective interventional case series of patients with RVO.[25] In the present study, use of other intravitreal corticosteroid (triamcinolone) was greatly reduced after the start of DEX implant treatment, and intravitreal triamcinolone was given to just 3.1% of the patients during the study period. Notably, the patient selection procedure for the study required that patients be treated with at least two injections of DEX implant. Patients who regained lost vision and whose macular edema resolved after receiving a single DEX implant injection would not have been included in the chart review.

As this study was a retrospective chart review of patients seen in actual practice, study limitations included the lack of randomization and the open-label treatment. The data collected for each patient varied based on the number of DEX implant injections received and the frequency and duration of follow-up, and information that could be useful was not always included on the patient chart. A minimum follow-up of longer than 3 months after the last DEX implant may have been preferable. Also, there was no standardization of assessments, and only the adverse events recorded on the patient charts were identified. Adjunctive treatments were allowed and must be acknowledged in the interpretation of the results. However, the study had the advantage that the study population was more inclusive than the study populations in previous large controlled studies of DEX implant and included both real-world treatment patterns and patients with complicated histories and comorbidities.

In summary, the results of this study demonstrate that the clinical use of two or more DEX implants, either alone or in combination with common adjunctive RVO treatments, is safe and effective in the treatment of macular edema after RVO. Decreases in macular edema and improvements in visual acuity continued to be seen after each subsequent DEX implant injection, and no new safety concerns developed after use of multiple implants.

Key words: corticosteroids, intravitreal injections, macular edema, optical coherence tomography, retinal vein occlusion, VEGF, visual acuity.

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References

1. Rehak M, Wiedemann P. Retinal vein thrombosis: pathogenesis and management. J Thromb Haemost 2010;8:1886–1894.
2. Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. Curr Eye Res 2008;33:111–131.
3. Mohamed Q, McIntosh RL, Saw SM, Wong TY. Interventions for central retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2007;114:507–519.
4. Daien V, Navarre S, Fesler P, et al. Visual acuity outcome and predictive factors after bevacizumab for central retinal vein occlusion. Eur J Ophthalmol 2012;22:1013–1018.
5. Coscas G, Loewenstein A, Augustin A, et al. Management of retinal vein occlusion—consensus document. Ophthalmologica 2011;226:4–28.
6. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984;98:271–282.
7. Central Vein Occlusion Study Group M. Evaluation of grid pattern photocoagulation for macular edema in central vein

occlusion. The Central Vein Occlusion Study Group M report. Ophthalmology 1995;102:1425–1433.
8. Hahn P, Fekrat S. Best practices for treatment of retinal vein occlusion. Curr Opin Ophthalmol 2012;23:175–181.
9. Ip MS, Scott IU, VanVeldhuisen PC, et al; SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. Arch Ophthalmol 2009; 127:1101–1114. Erratum in: Arch Ophthalmol 2009; 127:1648.
10. Haller JA, Bandello F, Belfort R Jr, et al; for the 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.
11. Haller JA, Bandello F, Belfort R Jr, et al; for the Ozurdex GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 2011;118:2453–2460.
12. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011;118:1594–1602.
13. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 2011;118:2041–2049.
14. Campochiaro PA. Anti-vascular endothelial growth factor treatment for retinal vein occlusions. Ophthalmologica 2012; 227(suppl 1):30–35.
15. 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.
16. Kuppermann BD, Blumenkranz MS, Haller JA, et al; Dexamethasone DDS Phase II Study Group. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol 2007;125:309–317.
17. Haller JA, Dugel P, Weinberg DV, et al. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. Retina 2009;29:46–51.
18. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing Snellen visual acuity measurements. Retina 2010;30: 1046–1050.
19. Blumenkranz MS, Haller JA, Kuppermann BD, et al. Correlation of visual acuity and macular thickness measured by optical coherence tomography in patients with persistent macular edema. Retina 2010;30:1090–1094.
20. Matonti F, Hoffart L, Baeteman C, Denis D. Repeated treatment for macular edema in vein occlusion by intravitreal implant of dexamethasone. Case Rep Ophthalmol 2012;3: 339–342.
21. Querques L, Querques G, Lattanzio R, et al. Repeated intravitreal dexamethasone implant (Ozurdex®) for retinal vein occlusion. Ophthalmologica 2013;229:21–25.
22. Jaissle GB, Szurman P, Feltgen N, et al; Retinal Vein Occlusion Study Group. Predictive factors for functional improvement after intravitreal bevacizumab therapy for macular edema due to branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol 2011;249:183–192.
23. Yeh WS, Haller JA, Lanzetta P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. Ophthalmology 2012;119:1190–1198.
24. Shilling JS, Jones CA. Retinal branch vein occlusion: a study of argon laser photocoagulation in the treatment of macular oedema. Br J Ophthalmol 1984;68:196–198.
25. Singer MA, Bell DJ, Woods P, et al. Effect of combination therapy with bevacizumab and dexamethasone intravitreal implant in patients with retinal vein occlusion. Retina 2012; 32:1289–1294.