Dexamethasone Implant for Diabetic Macular Oedema: 1-Year Treatment Outcomes from the Fight Retinal Blindness! Registry

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ORIGINAL RESEARCH

Dexamethasone Implant for Diabetic Macular Oedema: 1-Year Treatment Outcomes from the Fight Retinal Blindness! Registry

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ABSTRACT

Introduction: Phase III clinical trials of dexamethasone intravitreal implant for diabetic macular oedema (DMO) have reported significant improvements in visual acuity (VA). Studies evaluating the treatment of DMO in routine clinical practice provide data to identify areas that need improvement. This study evaluated 12-month treatment outcomes of dexamethasone implant for DMO in routine clinical practice.

Methods: Retrospective data analysis of eyes that started dexamethasone implant for DMO from 1 June 2013 to 30 April 2019 in routine clinical practice tracked in the Fight Retinal Blindness! Registry.

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Results: Of the 4282 eyes (2518 patients) that started DMO treatment in the specified period, 267 (6%) eyes (204 patients) received 454 dexamethasone implant injections. Two-fifths (106 eyes) had received prior treatment for DMO. The mean (95% confidence interval [CI]) VA change at 12 months was 1.8 (− 0.5, 4.2) letters from the mean (standard deviation [SD]) VA of 56.5 (19.8) letters at baseline, with 41% eyes achieving at least 20/40. The mean (95% CI) change in central subfield thickness over 1 year was − 79 (− 104, − 54) μm from a mean (SD) of 459 (120) μm at baseline. Eyes that completed 1 year of follow-up received a median (Q1, Q3) of 2 (1, 2) dexamethasone implants. One-tenth of phakic eyes received cataract surgery while 2% had a pressure response requiring anti-glaucoma medications.
Conclusions: One-year treatment outcomes of dexamethasone intravitreal implant for DMO in routine clinical practice were inferior to those in the clinical trials perhaps because of fewer treatments in clinical practice.

Keywords: Diabetic macular oedema; Dexamethasone; Real-world outcomes; Routine clinical practice

Key Summary Points

Why carry out this study?
Clinical trials reported that eyes with diabetic macular oedema on dexamethasone implant at 12 months had vision improvement similar to those on bevacizumab resulting from fewer treatments (median number of injections of 2.7 in the dexamethasone and 8.6 in the bevacizumab group).
Studies evaluating the outcomes of eyes that received dexamethasone implant for diabetic macular oedema in routine clinical practice provide data on whether they are similar to those in clinical trials and identify areas for improvement where they are not.

What was learned from this study?
Only 6% eyes received dexamethasone implant for diabetic macular oedema in routine clinical practice. These eyes had, in general, worse vision and thicker macula.
The outcomes at 12 months in eyes that received dexamethasone implant for diabetic macular oedema in routine clinical practice were inferior to clinical trials.
Eyes with diabetic macular oedema received fewer dexamethasone implants in routine clinical practice than indicated by clinical trial experience.

INTRODUCTION

The sustained release dexamethasone intravitreal implant (Ozurdex®; Allergan, Inc., Irvine, CA, USA) is recommended for the treatment of diabetic macular oedema (DMO) in pseudophakic eyes and in those where vascular endothelial growth factor (VEGF) inhibitors are contraindicated [1, 2]. It may be also considered when eyes with DMO have reduced vision and thickened maculae despite treatment with VEGF inhibitors, which a significant proportion of patients in the Diabetic Retinopathy Clinical Research Network clinical trials did after 6 months [3, 4]. Steroids last longer, reducing the burden of frequent clinical visits while on VEGF inhibitor treatments [5]. They may also treat the inflammatory component of DMO more effectively [6].

The Macular Edema Assessment of Implantable Dexamethasone in Diabetes (MEAD) study reported that dexamethasone implant was safe and effective for the treatment of DMO [7]. The intravitreal bevacizumab vs. intravitreal dexamethasone for DMO (BEVORDEX) study found that the proportion of eyes with vision improvement at 12 months was similar in the two groups from a mean number of injections of 2.7 in the dexamethasone and 8.6 in the bevacizumab group [8].

Some studies that reported the outcomes of the dexamethasone implant for DMO in routine clinical practice found that the implant was safe and effective in improving visual acuity and reducing macular thickness from a few injections [9–13]. This study aimed to report visual acuity, anatomic outcomes, proportion of eyes that received dexamethasone implant and the number of dexamethasone implants over the first year of treatment in eyes with DMO in routine clinical practice.

METHODS

Design, Data Sources and Measurements

This was a retrospective analysis of data collected in the prospectively designed web-based registry for tracking treatment outcomes of macular diseases—the Fight Retinal Blindness! Registry. The registry's DMO module, which was adapted from the age-related macular degeneration treatment outcomes module, collects data of eyes that receive treatment for DMO in routine clinical practice [14]. This module, initially implemented in Australia, New Zealand and Switzerland in April 2015, has expanded to countries in Europe and Asia. The present analysis included eyes from clinical practices in Australia, France, Italy and Spain.

The data recorded at each clinical visit include the number of letters read on a logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) chart, treatment given, the central subfield thickness (CST [μm]) measured using spectral-domain optical coherence tomography (OCT), the location of DMO (centre-involving, non-centre-involving or no DMO), procedures and ocular adverse events [15]. Duration and type of diabetes, grading of diabetic retinopathy (DR, Early Treatment Diabetic Retinopathy Study Report 9) and previous treatment for DMO were recorded at the baseline visit [16]. The data were available for subsequent analysis and reporting only when all the mandatory fields were entered, thereby starting a built-in validation process that checked whether all mandatory fields were completed and the values were within the predetermined ranges, for example, visual acuity had to be between 0 to 100 letters. Categorical variables, such as the grading of DR, had to be selected from a drop-down menu of pre-specified options. All treatment decisions, including choice of treatment and frequency of visits, were based on VA and OCT at the discretion of the practitioner in consultation with the patient, thereby reflecting routine clinical practice.

Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the French Society of Ophthalmology Institutional Review Board (Société Française d'Ophtalmologie Institutional Review Board), the Ethics Committee of the University of Milan and the Institutional Review Board of the Institut Clínic d'Oftalmología—Hospital Clinic of Barcelona. Ethics committees in Australia approved the use of "opt-out" patient consent. Informed consent ("opt-in consent") was sought from patients in France, Italy and Spain. This study adhered to the tenets of the Declaration of Helsinki.

Patient Selection

Eyes of patients with diabetes who had their first DMO treatment recorded in the FRB! Registry with dexamethasone implant (0.7 mg Ozurdex; Allergan, Inc., CA, USA) from 1 June 2013 to 30 April 2019, irrespective of whether they were previously treated for DMO or not, were included in the analysis. Eyes that completed at least 12 months of observations after the initial dexamethasone implant were defined as "completers". "Switchers" were eyes that switched treatment to VEGF inhibitors before completion of 12 months from the initial implant. Eyes that did not complete 12 months of observations were defined as "non-completers".

Outcomes

The main outcome was the mean change in VA at 12 months from the start of Ozurdex® treatment. Secondary outcomes were the mean

change in CST, frequency of treatments and visits, the proportion of eyes with VA ≥ 69 letters (20/40 Snellen equivalent) and ≤ 35 letters (20/200) and the proportion of eyes that gained ≥ 10 letters and those that lost ≥ 10 letters at 12 months. These outcomes were also analysed in eyes stratified by baseline VA into two groups, ≥ 69 letters (20/40) and ≤ 68 letters (20/50), to study the relationship of baseline VA on the outcomes, particularly the number of treatments and change in CST. We also compared the outcomes in eyes that were treatment-naïve and those that received prior treatment for DMO.

Statistical Analysis

Descriptive data included the mean (standard deviation), median (first and third quartiles) and percentages where appropriate. Eyes were considered to have been observed from the first treatment visit up to their 12-month visit (365 ± 30 days). Wilcoxon rank sum tests, *t* tests, chi-square tests and Fisher's exact tests were used as appropriate to compare baseline characteristics between pretreated and treatment-naïve eyes. Paired *t* tests were used to determine whether changes in VA and CST from baseline were significant.

We used a generalized additive model including data from completers, switchers (until the time of switch) and non-completers (last observation before the dropout) to display VA and CST over 12 months. We compared the outcomes of the dexamethasone implant in eyes that were treatment naïve with those that received prior DMO treatment in all eyes (completers, non-completers and switchers) using last observation carried forward. We compared the number of injections and visits in eyes stratified by initial VA and in treatment-naïve vs. previously treated eyes using quasi-Poisson regression models adjusted for age, VA, CST and clinically significant macular oedema (CSMO) activity at baseline, and nesting of outcomes within practice with an offset for log days of follow-up. Kaplan–Meier survival analysis was used to plot survival curves for time to non-completion.

All analyses were conducted using R version 4.0.2 (http://www.R-project.org/) with the lme4 package (V1.1–21) for mixed-effects regression analysis, mgcv package (V1.8–31) for generalized additive (mixed) model computation and survival package (V 2.38) for dropout analysis [17–19].

RESULTS

Study Participants

Of the 4282 eyes (of 2518 patients) that started treatment for DMO in the period tracked in the registry, 267 eyes (6%) of 204 patients started with dexamethasone implant, including 63 patients treated in both eyes. Patients that started DMO treatment with dexamethasone implant tended to be older with worse vision and thicker macula than those starting with VEGF inhibitors (supplementary material). Baseline characteristics of eyes in the dexamethasone implant group are summarized in Table 1. The mean (SD) age of the patients at the baseline visit was 68 (11) years. The mean (SD) VA and CST were 55.3 (20.8) letters (20/80 Snellen equivalent) and 456 (127) μm. Most had type 2 diabetes. Around two-fifths (40%) had received prior treatment for DMO. Prior treatments included VEGF inhibitors (33%), intravitreal triamcinolone (37%) and macular laser (61%). Eyes that were treatment-naïve and those that received prior treatment had similar baseline characteristics, except for the presence of severe forms of diabetic retinopathy, lower mean IOP and more pseudophakic eyes in the latter (Table 1).

Outcomes at 12 Months

Figure 1 illustrates the estimated mean VA and CST in all eyes from generalized additive models over 12 months. The mean VA peaked in the first 2 months during which a maximum reduction in the macular thickness was also observed. The mean VA and CST from the third month onwards tended to return towards the baseline.

Table 1 Demographic characteristics

	All eyes	Treatment-naïve eyes	Pretreated eyes	*p* value
Eyes, *n*	267	161	106	
Patients, *n*	204	133	82	
Female, *n* (%)	75 (37)	48 (36)	32 (39)	
Right eye, *n* (%)	133 (50)	84 (52)	49 (46)	
Pseudophakics, *n* (%)	75 (28)	38 (24)	37 (35)	0.050
Age years, mean (SD)	68 (11)	68 (11)	66 (12)	0.13
Diabetes duration years, mean (SD)	17 (10)	16 (9)	19 (12)	0.10
Diabetes type, %				
Type 1	4	5	3	0.25
Type 2	96	95	97	
Diabetic retinopathy, %				
Mild	27	34	17	
Moderate	34	36	30	< 0.001
Severe NPDR	13	14	12	
PDR non-high risk	17	13	22	
PDR high risk	10	4	19	
Baseline VA letters, mean (SD)	55.3 (20.8)	55.7 (21.3)	54.7 (20)	0.69
VA ≥ 69 letters, %	31	32	28	0.58
VA ≤ 35 letters, %	20	18	22	0.55
CST μm, mean (SD)	456 (127)	466 (129)	442 (123)	0.15
IOP mmHg, mean (SD)	15 (4)	16 (4)	14 (3)	0.057
CSMO grades, %				
Centre-involving	91	93	90	
Non-centre-involving	6	5	8	0.68
No CSMO	3	2	2	

n number, *SD* standard deviation, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *VA* visual acuity, *CST* central subfield thickness, *IOP* intraocular pressure, *CSMO* clinically significant macular oedema

Around two-thirds eyes completed 12 months of follow-up from the initial dexamethasone implant. The mean (95% confidence interval) VA change at 12 months was 1.8 (− 0.5, 4.2) letters ($p = 0.13$, Table 2). The proportion of eyes with VA ≥ 69 letters (20/40) improved to 41% at 12 months from 36% at baseline ($p < 0.001$). Around 27% of the cohort gained ≥ 10 letters at 12 months while 15% lost ≥ 10 letters (Table 2). The mean (95%CI) change in CST over 12 months was − 79 (− 104, − 54) μm from a mean of 459 (120) μm at baseline ($p < 0.001$). Eyes received a median (Q1, Q3) of 2 (1, 2) dexamethasone implants

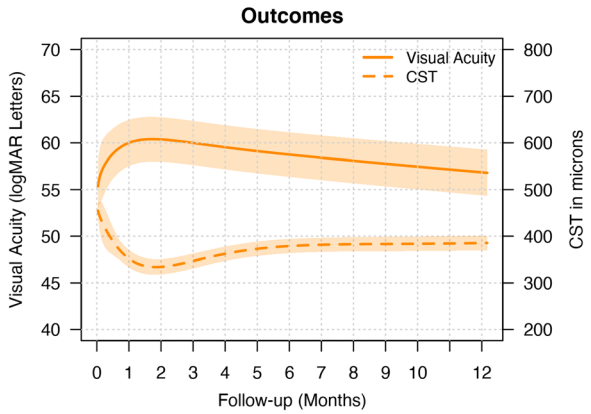

Fig. 1 Line graphs showing the mean visual acuity (orange solid line) in logMAR letters (y-axis) and central subfield thickness (orange dashed line) in microns (z-axis) in Ozurdex-treated eyes over 12 months irrespective of whether or not they completed 12 months of observations. The orange shaded area represents the 95% confidence interval

from a median (Q1, Q3) of 6 (5, 8) visits over 12 months. Fifty-seven eyes (37%) received only one dexamethasone implant, 64 eyes received two implants, at a median (Q1, Q3) interval of 168 (119, 267) days, and 14 eyes received three implants, at 280 (244, 327) days interval, while 20 eyes received three or more dexamethasone implants in the 12 months (Table 2). Very few (6%) eyes required additional treatments, including macular laser and intravitreal steroid injections (triamcinolone acetonide), during the 12 months (Table 2).

Table 3 compares the outcomes of the dexamethasone implant in the treatment-naïve eyes vs. those that received prior treatment. The mean (95% CI) VA change of 2.5 (0, 5) letters at 12 months in the treatment-naïve eyes was similar to 3.2 (0.5, 5.9) letters in the pretreated eyes ($p = 0.72$), as was the mean (95% CI) change in CST of − 86 (− 121, − 51) µm to − 70 (− 105, − 35) µm in the pretreated group ($p = 0.14$). Eyes in both groups received similar median (Q1, Q3) number of dexamethasone implants, 1 (1, 2) vs. 2 (1, 2; $p = 0.56$) in pretreated eyes, from similar median (Q1, Q3) visits, 6 (4, 8) vs. 5 (4, 7; $p = 0.36$, Table 3).

Eyes completing 12 months of follow-up were divided into two groups according to the VA at baseline, good initial vision (VA ≥ 69 letters; 52 eyes [34%]) and VA ≤ 68 letters (103 eyes [66%]), to study the effect of the initial vision on the outcomes (Table 4). The mean (95% CI) VA change at 12 months in the initial VA ≤ 68 letters group of 4.2 (1.1, 7.3) letters from 46.8 (17.3) letters at baseline was significant ($p < 0.05$) while those in the initial good vision group, − 2.9 (− 6.3, 0.5) letters from a mean (SD) of 75.6 (4.6) letters at baseline, was not ($p = 0.08$). The maculae in eyes with initial VA ≤ 68 letters was thicker at baseline (mean CST of 491 µm vs. 402 µm in the VA ≥ 69 letters group, $p < 0.001$) and remained so at 12 months (399 µm vs. 342 µm, $p = 0.01$). Eyes in both group received similar median (Q1, Q3) number of dexamethasone implants, 2 (1, 2) in the VA ≥ 69 letters group vs. 2 (1, 2; $p = 0.78$), which resulted from similar median (Q1, Q3) visits, 6 (5, 9) vs. 7 (5, 8; $p = 0.77$, Table 4).

Treatment Switch

Fifty-two eyes (19%, treatment-naïve—33 [22%] and pretreated—19 [18%]) on dexamethasone implant switched treatment to VEGF inhibitors over 12 months. Most of the switches were to aflibercept (29 eyes), followed by ranibizumab (15 eyes) and bevacizumab (8 eyes). The median (Q1, Q3) time to switch was 180 (119, 273) days. The mean (95% CI) change in VA and CST at the time of switch was similar to those that completed 12 months on dexamethasone implant injection, 3.8 (− 0.7, 8.4) vs. 1.8 (− 0.5, 4.2) letters ($p = 0.43$) and − 76 (− 122, − 29) vs. − 79 (− 104, − 54) µm ($p = 0.34$) in completers. The mean (95% CI) IOP at the time of switch, 19 (17, 21), in the switchers was significantly higher than at baseline, 14 (12, 17; $p < 0.001$). The mean (95% CI) 12-month VA change in the 48/52 switchers that went on to complete 12 months of follow-up was 2.5 (− 0.4, 5.4) letters ($p = 0.09$) after a median (Q1, Q3) of 3 (2, 4) injections while the mean CST change was − 19 (− 45, 6) µm ($p = 0.14$).

Non-Completion Rate at 12 Months

Sixty eyes (22%, treatment-naïve—40 [25%] and pretreated—20 [19%]) were lost to follow-up

Table 2 Outcomes at 12 months

	Completers	Switchers	Non-completers
Eyes, *n*	155	52	60
Patients, *n*	126	47	47
Baseline VA letters, mean (SD)	56.5 (19.8)	58.4 (18.8)	49.5 (23.9)
Final VA letters, mean (SD)	58.3 (20.3)	62.3 (16.7)	53.9 (22.4)
Change VA letters, mean (95% CI)	1.8 (− 0.5, 4.2)	3.8 (− 0.7, 8.4)	4.4 (0.5, 8.2)
Gain ≥ 10 letters %	27	31	30
Loss ≥ 10 letters %	15	21	7
VA ≥ 69 letters %, baseline/final	36 / 41	29 / 44	25 / 30
VA ≤ 35 letters %, baseline/final	17 / 17	14 / 8	30 / 22
IOP mmHg, baseline/final	15 / 16	14 / 19	15 / 16
Baseline CST µm, mean (SD)	459 (120)	434 (139)	467 (134)
Final CST µm, mean (SD)	379 (137)	361 (100)	357 (118)
Change CST µm, mean (95% CI)	− 79 (− 104, − 54)	− 76 (− 122, − 29)	− 108 (− 140, − 76)
Dexamethasone, median[a] (Q1, Q3)	2 (1, 2)	1 (1, 1)	1 (1, 2)
1 Dexamethasone implant, *n* (%)	57 (37)	42 (81)	38 (63)
2 Dexamethasone implants, *n* (%)	64 (41)	9 (17)	20 (33)
3 Dexamethasone implants, *n* (%)	14 (9)	1 (2)	2 (3)
≥ 3 Dexamethasone implants, *n* (%)	20 (13)	0	0
Additional laser, *n*	8	2	0
Additional triamcinolone, *n*	1	0	0
Visits, median (Q1, Q3)	6 (5, 8)	5 (4, 6)	4 (3, 6)

n number, *VA* visual acuity, *SD* standard deviation, *CI* confidence interval, *CST* central subfield thickness, *Q1* first quantile, *Q3* third quantile, *IOP* intraocular pressure, *Completers* eyes with 12 months of observation from the start of treatment, *Switchers* eyes that switched to VEGF inhibitors before completing 12 months, *Non-completers* eyes not completing 12 months of observations from the start of treatment

[a]The distribution of the total number of dexamethasone implants over 12 months was skewed to the left

before completing 12 months observations (Fig. 2). The median (Q1, Q3) time to dropout was 135 (76, 215) days. These eyes at baseline had worse vision than those that completed 12 months of observations (mean VA of 49.5 letters vs. 56.5 letters in completers; $p = 0.05$, Table 2). Their mean (95% CI) VA change from the start of treatment to their last visit of 4.4 (0.5, 8.2) letters was similar to 1.8 (– 0.5, 4.2) letters observed at 12 months in completers ($p = 0.26$), as was the mean VA at their last visits, 53.9 letters vs. 58.3 letters in completers ($p = 0.19$; Table 2). The mean CST at baseline was similar in both completes and non-completers (467 µm. vs. 459 µm, $p = 0.71$). The mean CST (95% CI) change at the last visit in the non-completers was − 108 (− 140, − 76) µm, similar to − 79 (− 10.4, − 54) µm at 12 months in completers ($p = 0.16$). These eyes

Table 3 Outcomes stratified by prior treatment status

	Treatment-naïve	Pretreated	*p* value
Eyes, *n*	161	106	
Patients, *n*	133	82	
Baseline VA letters, mean (SD)	55.7 (21.3)	54.7 (20)	0.69
Final VA letters[a], mean (SD)	58.2 (20.5)	57.9 (20)	0.90
Change VA letters[a], mean (95% CI)	2.5 (0, 5)	3.2 (0.5, 5.9)	0.72
Baseline CST, µm (SD)	466 (129)	442 (123)	0.20
Final CST[a], µm (SD)	371 (126)	371 (127)	0.98
Change CST[a], µm (95% CI)	− 95 (− 121, − 69)	− 69 (− 94, − 44)	0.15
Dexamethasone[a], median[b] (Q1, Q3)	1 (1, 2)	2 (1, 2)	0.56[c]
1 Dexamethasone implant, *n* (%)	85 (53)	52 (49)	
2 Dexamethasone implants, *n* (%)	58 (36)	35 (33)	
3 Dexamethasone implants, *n* (%)	8 (5)	9 (9)	
≥ 3 Dexamethasone implants, *n* (%)	10 (6)	10 (10)	
Additional laser[a], *n*	9	1	0.10
Additional Triamcinolone[a], *n*	0	1	0.40
Visits[a], median (Q1, Q3)	6 (4, 8)	5 (4, 7)	0.36[c]

n number, *VA* visual acuity, *SD* standard deviation, *CI* confidence interval, *CST* central subfield thickness, *Q1* first quantile, *Q3* third quantile

[a]Last observation carried forward for switchers and non-completers

[b]The distribution of the total number of dexamethasone implants over 12 months was skewed to the left

[c]Calculated from quasi-Poisson regression model adjusted for age, VA, CST and CSMO activity at baseline and practice with log days of follow-up included as an offset variable

received a median (Q1, Q3) of 1 (1, 2) dexamethasone implants from 4 (3, 6) visits (Table 2).

Adverse Events

A total of 454 dexamethasone implants were administered in the 267 eyes over the 12 months. Nineteen (10%) phakic eyes received cataract surgery during the observed period. Intraocular pressure-lowering medication was required in 11 (2%) eyes. Infectious endophthalmitis, the most serious adverse event associated with intraocular injections, was not observed in the study cohort.

DISCUSSION

We found that few (6%) eyes started dexamethasone implant for DMO in routine clinical practice. Eyes that received prior treatment for DMO, except for the severe diabetic eye disease, were similar to the treatment-naïve eyes at baseline. The mean VA improvement and CST reduction were greatest in the first 2 months of treatment, after which they tended to regress towards the baseline. The overall mean VA gain of 1.8 letters at 12 months from 56.5 letters at baseline was not significant despite a significant reduction in the mean CST of 79 µm from 459 µm. Eyes with VA ≥ 69 letters (20/40) increased from 36% at baseline to 41% at

Table 4 Outcomes stratified by visual acuity at presentation

	Visual acuity ≥ 69 letters (20/40 or better)	Visual acuity ≤ 68 letters (20/50 or worse)	*p* value
Eyes, *n*	52	103	
Patients, *n*	49	87	
Baseline VA letters, mean (SD)	75.6 (4.6)	46.8 (17.3)	
Final VA letters, mean (SD)	72.7 (12.2)	51 (19.6)	< 0.001
Change VA letters, mean (95% CI)	− 2.9 (− 6.3, 0.5)	4.2 (1.1, 7.3)	0.002
Gain ≥ 10 letters %	4	39	< 0.001
Loss ≥ 10 letters %	15	15	1
Baseline CST µm, mean (SD)	402 (82)	491 (127)	< 0.001
Final CST µm, mean (SD)	342 (109)	399 (146)	0.01
Change CST µm, mean (95% CI)	− 60 (− 80, − 31)	− 90 (− 125, − 54)	0.20
Dexamethasone, median[a] (Q1, Q3)	2 (1, 2.2)	2 (1, 2)	0.78[b]
1 Dexamethasone implant, *n* (%)	19 (37)	38 (37)	
2 Dexamethasone implants, *n* (%)	20 (38)	44 (43)	
3 Dexamethasone implants, *n* (%)	5 (10)	9 (8)	
≥ 3 Dexamethasone implants, *n* (%)	8 (15)	12 (12)	
Additional laser, *n*	3	5	1
Additional Triamcinolone, *n*	0	1	1
Visits, median (Q1, Q3)	6 (5, 9)	7 (5, 8)	0.77[b]

n number, *VA* visual acuity, *SD* standard deviation, *CI* confidence interval, *CST* central subfield thickness, *Q1* first quantile, *Q3* third quantile

[a]The distribution of the total number of dexamethasone implants over 12 months was skewed to the left

[b]Calculated from quasi-Poisson regression model adjusted for age, VA, CST and CSMO activity at baseline and practice with log days of follow-up included as an offset variable

12 months while 27% of eyes gained ≥ 10 letters. Eyes with good initial vision, VA ≥ 69 letters (20/40), tended to maintain vision. Eyes received a median of 2 dexamethasone implants over 12 months. The outcomes in the treatment-naïve and pretreated eyes were similar. One-fifth (19%) switched treatment to VEGF inhibitors, possibly because of an increase in IOP from baseline at the time of switch. One-fifth (22%) dropped out before completion of 12 months of observation. These eyes had gained a mean of 4.4 letters after a median of 1

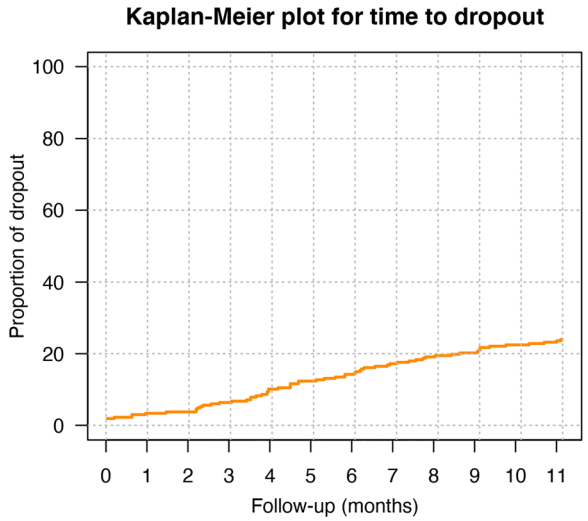

Fig. 2 Kaplan–Meier plot for time from starting treatment to dropout in eyes treated with dexamethasone over 12 months

dexamethasone implant before they dropped out. Switchers and non-completers were similar in both treatment-naïve and pretreated groups.

We observed that the change in the mean VA and CST peaked in the first 2 months after insertion of the implant which is consistent with reports from the randomized clinical trials of dexamethasone implant for DMO [7, 8]. The mean change in VA of + 1.8 letters at 12 months in the present study from a mean of 56.5 letters at baseline was lower than the mean gain of 5.6 letters from a mean of 55.5 letters at baseline of eyes in the dexamethasone group in the BEVORDEX study [8]. Fewer eyes (27%) in the present study gained ≥ 10 letters at 12 months than the dexamethasone cohort in the BEVORDEX study (41%) [8]. The mean VA at 1 year in the present study (58.3 letters) was lower to that of the dexamethasone group in the BEVORDEX study (61 letters), suggesting an inferior treatment outcome in routine clinical practice than in the clinical trial. Eyes in the present study received fewer (median of 2) dexamethasone implants over 12 months than the BEVORDEX cohort (2.7), which is the likely reason for the inferior outcomes.

The BEVORDEX study reported that dexamethasone effectively reduced macular thickness of DMO eyes [8]. Eyes in the present study had a significant reduction of macular thickness with dexamethasone implant treatment which was observed in both strata of VA at the initiation of treatment. Eyes in both treatment-naïve and previously treated groups had a similar reduction in mean macular thickness at 12 months. The mean CST change of − 79 μm at 12 months from the mean CST of 449 μm at baseline was, however, lower than the mean reduction of 187 μm from 474 μm at baseline of the dexamethasone cohort in the BEVORDEX study [8]. Again, the reasons for inferior outcomes may be because our patients received fewer treatments than those in the clinical trial [8].

Cataract and increased IOP are expected complications of steroid treatments, the incidence rates of which differ with the type of steroid and the duration of treatment [7, 20, 21]. Around 10% of phakic eyes underwent cataract surgery over 12 months in the present study, which was slightly higher than that of the dexamethasone cohort in the first year of the BEVORDEX study (6.5%) [8]. The patients in the present study were older (mean age of 68 years) than those that received dexamethasone implant in the BEVOREX study (62 years), which could account for the higher rate of cataract surgery we observed. Other reasons could be related to the difference in the inclusion/exclusion criteria of clinical trials. Very few eyes (2%) in the present study had an IOP rise over 12 months that required medications; this was likely under-reported.

A few studies have evaluated treatment outcomes of dexamethasone implant for DMO in routine clinical practice after 12 months from the start of treatment [9, 12, 13, 22]. These studies have reported a mean VA gain ranging from + 4.2 to + 11.5 letters after 1 year of treatment from a mean of 51 to 55 letters at baseline and a mean CST reduction of 80 to 315 μm from 450 to 583 μm at baseline [9, 12, 22]. The mean VA of 55.3 letters and the mean CST of 459 μm at baseline in the present study were better than these studies. The mean VA 1 year after the start of treatment, which is the most important concern for the patient, in these studies ranged from 54.7 to 66.5 letters while the mean CST ranged from 268 to 370 μm. The VA gain of + 1.8 letters in the

present study was one of the lower gains reported by other observational studies; however, the mean VA of 58.3 letters at 1 year was one of the better 12-month VA outcomes [9, 12, 22]. The mean macular thickness of 379 μm at 12 months in the present study, one of the worst 12-month anatomical outcomes in observational studies, suggests undertreatment though factors other than macular thickness affect VA in eyes with DMO [23].

Physicians may switch treatments for a variety of reasons including adverse or non-response to the current treatment [24]. Approximately one-fifth of eyes on dexamethasone implant in the present study switched to VEGF inhibitors after a median of 180 days. The mean VA and CST at baseline in the switchers were similar to those that completed 12 months on dexamethasone implant monotherapy. We did not observe improvement in vision and reduction of macular thickness following treatment switch from dexamethasone implant to VEGF inhibitors.

Participants that drop out or switch treatment in observational studies may introduce bias on treatment outcomes because these patients may be lost as a result of poor outcomes. Some eyes (22%) in the present study were lost before completing 12 months of observations from the start of dexamethasone implant treatment. These eyes had a higher VA gain than those that completed 12 months of observations, suggesting that non-compliance to treatment could be related to reasons other than poor outcomes [25].

The limitations of this study are inherent to those of observational studies. Treatment decisions in routine clinical practice, in contrast to those in the clinical trials, are not adjudicated from a reading centre or guided by protocols. Selection of cases and treatment regimen may also differ among physicians and from clinical trials. Only a small proportion (6%) of eyes in the registry started DMO treatment with dexamethasone implant. Information on the morphological characteristics of DMO, the reasons for the choice of dexamethasone implant for DMO in the cohort, treatment switching and those for re-treatment intervals cannot be deduced from the data available. The results we report could be confounded by the previous treatments that two-fourths of our cohort had received prior to the dexamethasone implant; however, we did not observe any meaningful differences in the outcomes of pretreated and treatment-naïve eyes. Inclusion of paired eyes in our cohort may affect the outcomes because DMO depends on systemic status. Nevertheless, this study reports the treatment outcomes of dexamethasone implant as it was used in routine clinical practice. Imputation of missing data with the last observation carried forward for non-completers makes the assumption that their VA does not improve or decline further, which may not be appropriate for DMO. For transparency, we have reported the outcomes of non-completers separately without imputation, noting that non-completers gained slightly more vision but finished with lower VA than completers.

CONCLUSIONS

This study found that the dexamethasone implant generally maintained vision at 12 months in eyes with DMO in routine clinical practice. Treatment with the steroid implant was relatively safe. A few eyes on dexamethasone implant treatment had IOP elevation that required treatment and a few others had cataract surgery during the 12 months. The outcomes we observed were inferior and treatments fewer compared to those of clinical trials. Future observational studies may determine whether clinical outcomes can be improved with a modified, more intensive treatment regimen for the dexamethasone implant.

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Data Availability. Data are not publicly available. The statistical analysis plan can be obtained on request.

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