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ORIGINAL ARTICLE

Long-Term Intravitreal Dexamethasone Treatment in Eyes with Pretreated Chronic Diabetic Macular Edema

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Abstract

Purpose: The aim of this study is to assess the effect of repeated injections of dexamethasone implants in patients with persistent diabetic macular edema (DME) despite prior therapies.
Methods: This retrospective interventional study involved 47 DME-afflicted eyes, which were administered ≥2 intravitreal injections of dexamethasone. Group 1 (34 eyes) received a dexamethasone monotherapy, whereas group 2 (13 eyes) received a combination therapy with intravitreal antivascular endothelial growth factor as needed. The duration of dexamethasone effect until retreatment and the change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were defined as outcome measures.
Results: A total of 197 injections of dexamethasone were administered in group 1 and 52 in group 2 during a mean follow-up of 23 ± 10 and 24 ± 13 months, respectively. Mean time to reinjection was 4.6 ± 0.5 (group 1) and 5.3 ± 1.0 months (group 2; $P = 0.17$). Reinjection intervals did not shorten over time for up to 10 dexamethasone injections per eye in group 1 and BCVA improved from before 1 month after the first implantation, 7.0 letters ($P = 0.04$). In group 2, there was no significant improvement in BCVA at any time point. CRT decreased from 534 ± 208 and 529 ± 215 μm to 287 ± 115 and 371 ± 78 μm at 3 months and increased to 460 ± 186 μm and 547 ± 175 μm before reinjection (groups1 and 2, respectively). The maximal CRT before each implantation remained stable over time.
Conclusions: In eyes with chronic DME that respond incompletely to prior therapy or require frequent reinjections, dexamethasone shows promising long-term anatomic and functional improvement. The absence of a treatment effect reduction over time argues against a relevant rebound phenomenon.

Keywords: diabetic macular edema, DME, pretreatment, long-term treatment, dexamethasone intravitreal implant

Introduction

The pathophysiology of diabetic macular edema (DME) includes multiple growth factors such as vascular endothelial growth factor (VEGF) and inflammatory mediators. The intravitreal handling of DME with drugs began with the use of steroids, among which triamcinolone was first and foremost.[1] However, administration of these agents is associated with undesirable side effects, such as the progression of cataracts and secondary rises in intraocular pressure (IOP),[2] and although short-term results were usually satisfying, the favorable response was not perpetuated over longer periods. This less than optimal situation served as a bed of fertility for the advent of anti-VEGF therapy, which has since become the standard treatment regime. However, although anti-VEGF agents are locally well tolerated, the necessity for frequent reinjections and the unpredictability of the long-term outcome are to be counted among the drawbacks of the approach.[3] In some eyes, the response to anti-VEGF therapy is insufficient.[4] The reasons thereof are multifactorial, including loss of efficacy over time (tachyphylaxis/tolerance),[5,6] insufficient compliance due to frequent injection intervals, and

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VEGF being not the only relevant factor in the pathophysiology of the disease. There is evidence that these eyes benefit from treatment with dexamethasone implants.[4,7–9] The intravitreal glucocorticoid agents, triamcinolone and dexamethasone, could not hinder progression of early diabetic retinopathy (DRP) to the proliferative stage.[5,10] However, the portion of patients experiencing improvement in visual acuity, central retinal thickness (CRT), and dye leakage in fluorescein angiography is significantly higher than in untreated patients.[11] With respect to the functional outcome and CRT, dexamethasone and anti-VEGF agents would appear to be equally efficacious in the treatment of chronic and persistent DME.[12]

In this study, we assessed the effects of repeated injections (≥2–25) of dexamethasone in refractory, pretreated, and vitrectomized eyes with persistent and chronic DME.

Patients and Methods

This study was approved by the local institutional ethics committees in Bern (Kantonale Ethikkommission Bern) and Zurich (Kantonale Ethikkommission Zürich) with the reference number: 330/14 and was undertaken with the informed written consent of each of the participants, strictly following the tenets of the Declaration of Helsinki. Power analysis was performed.

The study was designed as a retrospective interventional case series in patients with chronic DME insufficiently responding to prior anti-VEGF therapy. DME that persisted over 6 months despite regular anti-VEGF treatment every 4–6 weeks with a CRT of over 250 μm was considered as persistent DME.

The decision to medication switch was based on deficient reduction of CRT or dissatisfying shortening of injection intervals under anti-VEGF monotherapy for every individual, respectively. Inclusion criterion was chronic DME over 6 months without complete resolution despite prior treatment with bevacizumab (Avastin®) and/or ranibizumab (Lucentis®; both Genentech, South San Francisco). Exclusion criteria were clinically not sufficiently controlled glaucoma, clear lens in young age, structural damage to the macula excluding functional gain, instable retinal detachment, and any systemic disease interfering with the local situation (ie, systemic vasculitis). All eyes were switched to the 0.7 mg dexamethasone implant (Ozurdex® Allergan Pharmaceuticals, Westport, Ireland), which was injected intravitreally on at least 2 separate occasions, on a pro re nata (PRN) basis and retreatment was only performed when needed. Retreatment was initiated in the case of a relevant increase in CRT (>250 μm) and/or a vision loss of more than 5 letters.

Group 1 received dexamethasone monotherapy, whereas group 2 received a combination therapy with anti-VEGF (either ranibizumab or aflibercept; Eylea@, Bayer, Berlin, Germany). The dexamethasone implant was provided in most cases as an off-label treatment (before approval for DME in Switzerland).

Measurements of best-corrected visual acuity (BCVA) were performed in ETDRS letters (when necessary, BCVA was determined on a logarithmic scale and converted to ETDRS letters; conversion between different notations was performed regarding the ranges of vision loss defined in ICD-9-CM); CRT [determined in μm by OCT, (Spectralis™; Heidelberg Engineering, Heidelberg, Germany)] and IOP (Goldmann applanation tonometry) were measured before the first and each following injection of dexamethasone, 1 and 3 months thereafter, and before reinjection. The primary endpoint was the duration of dexamethasone effect and the intervals between Ozurdex implantation. Duration of effect was defined as the time after dexamethasone implantation during which a stable situation (CRT of less than 250 μm and visual stability) was maintained until recurrence of intraretinal fluid.

Thirteen of 47 eyes received anti-VEGF treatment in between the dexamethasone implantations due to insufficient anatomic and functional response to monotherapy and were therefore analyzed separately (group 2). In group 2, the duration of effect was measured until any next intravitreal reinjection/reimplant. Secondary endpoints were the change in BCVA and CRT from before the switch to the dexamethasone implant to 3 months of follow-up after each implantation.

Eighty-eight percent of patients in group 1 and 92% in group 2 were treated for hypertension. None of the patients of groups 1 and 2 were documented as smoking.

The numerical data are presented as mean values together with the standard deviation and were statistically evaluated using Student's *t*-test. Where necessary, multilevel testing (MPlus, Version 7.2) was applied.[13]

Results

During the study period, 197 (group 1) and 52 (group 2) injections of dexamethasone were administered to 34 eyes in 28 patients (group 1, mean: 5.8; range: 2–25) and to 13 eyes in 10 patients (group 2, mean: 4.0; range 2–7) during a mean follow-up period of 23 ± 10 months (group 1: range: 6–43 months) and 24 ± 13 months (group 2: range: 12–48 months; Tables 1 and 2). The mean age of the patients was 66 ± 12 years in group 1 (range: 36–84 years) and 67 ± 13 years in group 2 (range: 44–89 years; $P = 0.8$).

In group one, 25 of the eyes, and in group two, 12 of the eyes were pseudophakic before receipt of the first injection of dexamethasone, by which time 5 (group 1: 14.7%) and 2 of the eyes (group 2: 15.4%) had undergone vitrectomy with a view to bringing the chronic DME under control.

Before intravitreal dexamethasone treatment, a total of 296 (mean: 8.7 ± 6.5; group 1) and 89 (mean: 6.8 ± 4.5; group 2) injections of an anti-VEGF agent had been administered over 24.7 ± 23.7 (group 1) and 18.3 ± 9.9 (group 2) months. The last anti-VEGF injection had been given on average 4.8 ± 7.1 and 3.7 ± 2.8 (groups 1 and 2, respectively) months before the switch. In group two, 5.3 ± 3.3 anti-VEGF injections were given in between dexamethasone implantations.

The functional and anatomical response to treatment with dexamethasone compared with before the switch was sustained on average for 4.6 ± 1.6 (group1) and 3.5 ± 1.7 (group 2; $P = 0.07$) months. Mean time to reinjection was 4.6 ± 0.5 (group 1) and 5.4 ± 1.2 months (group 2; $P = 0.09$; Fig. 1a). Although the number of eyes does not allow to assess the stability of treatment intervals that separated the 1st, 2nd, 3rd until >10th injection, these did not differ intraindividually ($P = 0.35$) in group 1, but were different interindividually ($P = 0.04$). Reinjection intervals did not shorten over time for up to 10 dexamethasone injections per eye in group 1, therefore arguing against a loss of efficacy over

Table 1. Information Appertaining to the 34 Diabetic Macular Edema-Afflicted Dexamethasone Monotherapy-Treated Eyes

Eyes	*Age*	*Duration of diabetes (years)*	*Duration of DME since diagnosis (years)*	*Number of previous injections*	*Time since last anti-VEGF injection until first Dex (months)*	*Vitrecto-mized y/n*	*Number of Dex injections*	*Time under Dex (follow-up in months)*	*BCVA before first injection (ETDRS letters)*	*IOP before first injection*	*CRT before first injection*	*BCVA 3 months after last Dex (ETDRS letters)*	*IOP 3 months after last Dex*	*CRT 3 months after last Dex*
1	47	40	8.5	20	2.5	y	25	42	54	2	676	65	14	565
2	47	40	8.5	29	0.5	n	24	43	95	6	242	100	10	203
3	73	20	6.5	9	0.75	y	2	23	89	12	457	90	14	380
4	73	20	6	12	1.5	y	10	38	100	19	384	100	17	258
5	54	30	14	7	3	y	8	38	70	10	778	90	14	208
6	73	51	13.8	15	1.5	n	12	42	80	18	208	90	25	200
7	73	51	3	9	1	n	7	24	85	18	453	100	14	320
8	60	28	4	18	2	n	3	21	85	18	280	90	17	252
9	71	23	3.4	6	6	n	6	35	65	18	490	100	19	249
10	61	13	1.5	12	3	n	2	28	80	15	444	85	16	296
11	82	17	4	15	1.5	n	2	27	74	15	455	85	11	347
12	70	15	2.7	12	3	y	2	18	70	13	299	70	11	253
13	70	8	0.6	4	5.5	n	5	15	60	8	781	75	7	374
14	84	16	9.2	7	41	n	2	6	85	12	611	95	17	210
15	80	30	4.6	7	13	n	2	6	90	15	525	90	14	233
16	69	15	4.8	14	14	n	3	8	70	17	657	85	18	176
17	73	19	1.5	6	1	n	3	15	85	18	211	85	20	181
18	56	13	10	20	4.5	n	4	18	30	12	557	35	9	500
19	67	4	0.5	3	2.5	n	6	28	35	15	723	45	11	338
20	70	5	0.6	5	1	y	4	16	70	14	441	85	16	323
21	69	12	1	2	4	n	4	27	50	14	338	100	12	315
22	75	6	0.6	3	3	n	5	20	45	13	756	65	16	233
23	81	15	1.9	3	1.5	n	4	17.5	65	12	349	85	19	222
24	36	20	4	2	1.5	n	5	18	50	12	512	35	19	248
25	48	18	2.5	12	4	n	6	23	78	16	638	85	13	253
26	63	13	2	3	3	n	5	25	50	12	638	75	13	176
27	60	12	2.3	3	4	n	5	23	35	8	1037	50	21	191
28	76	19	3.8	2	5	n	6	26	35	13	816	50	15	147
29	66	7	2.6	13	8	n	4	18	65	13	903	90	20	215
30	47	9	2.6	8	8	n	4	17	50	11	770	95	20	232
31	72	11	1.2	4	3	n	4	13	85	12	330	85	12	331
32	73	6	1.3	3	3	n	5	18	75	15	598	75	12	604
33	66	6	2	4	1.5	n	4	23	95	19	394	95	19	352
34	81	16	1.5	4	6	n	4	17	95	10	390	95	10	381
Average (1–34)	67.1	16.8	4.0	8.7	4.8	6 y/28 n	5.8	22.8	69	13	534	81	15	287

BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema; IOP, intraocular pressure; VEGF, vascular endothelial growth factor.

Table 2. Information Appertaining to the 13 Diabetic Macular Edema-Afflicted Combination Therapy-Treated Eyes

Eyes	*Age*	*Duration of diabetes (years)*	*Duration of DME since diagnosis (years)*	*Number of previous injections*	*Time since last anti-VEGF injection until first Dex (months)*	*Vitrecto-mized y/n*	*Number of Dex injections*	*Time under Dex (follow-up in months)*	*BCVA before 1st injection (ETDRS letters)*	*IOP before 1st injection*	*CRT before 1st injection*	*BCVA 3 months after last Dex (ETDRS letters)*	*IOP 3 months after last Dex*	*CRT 3 months after last Dex*
1	63	9	2.9	11	2	n	6	48	60	18	409	54	14	335
2	89	16	1	3	4.5	n	3	12	50	15	626	50	19	354
3	66	12	6	11	2.5	y	4	14	95	16	492	95	18	538
4	81	20	3.9	6	2.5	n	3	15	95	17	510	95	34	292
5	61	11	2.3	4	6	n	7	33	70	19	285	85	18	200
6	78	18	9.4	13	1.3	n	6	39	80	15	483	75	11	301
7	67	15	1	3	2	n	2	12	75	17	505	75	16	481
8	67	15	0.5	3	2.5	n	4	16	80	16	352	85	19	386
9	44	12	2	6	1.2	n	3	15	54	15	647	50	9	176
10	44	12	2	13	1.2	y	3	15	54	13	248	50	9	215
11	57	13	5	12	4.5	n	3	18	50	11	731	70	16	232
12	80	10	1	2	6.5	n	4	39	54	10	1079	60	10	265
13	67	8	1.5	2	11	n	4	35	54	11	510	50	10	305
Average (1–13)	68.5	13.1	3.0	6.8	3.7	2 yes/11 no	4	24	67	15	529	69	16	314

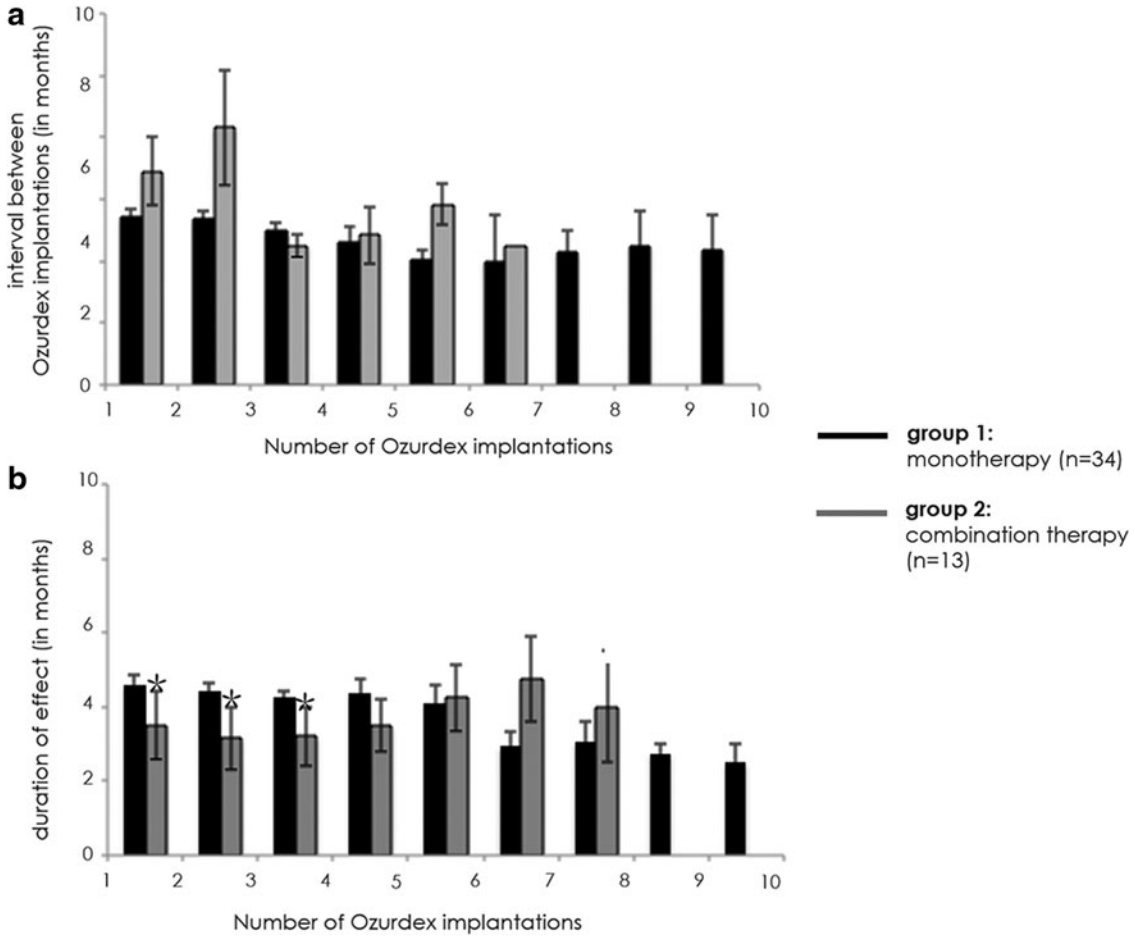

FIG. 1. Interval and effect duration between Ozurdex® implantations: **(a)** Interval between the Ozurdex implantations (in months) from first to 10th implantation per eye. **(b)** Duration of effect (in months) from first to 10th implantations per eye. *Black*: group 1 ($n=34$ eyes in 28 patients); *gray*: group 2 ($n=13$ eyes in 10 patients); $^*P \leq 0.05$. Error bars represent the standard error of the mean (SEM).

time, whereas in group 2, the intervals differed intra-individually ($P=0.02$), but not interindividually ($P=0.2$), most likely due to insufficient anatomic and functional response to monotherapy with irregular need of anti-VEGF agents in between dexamethasone implantations. Regarding the duration of effect, namely the time until recurrence of macular edema, the interval was significantly shorter in group 2 than in group 1 for the first 3 implantations (Fig. 1b).

Mean BCVA (ETDRS letters) improved in group 1 from 69 ± 20 before the first injection of dexamethasone to 80 ± 16 ($P=0.04$) and 81 ± 14 ($P=0.007$) 1 and 3 months later and to 76 ± 20 before the first reinjection ($P=0.15$). In group 2, the BCVA stabilized from 68 ± 17 to 71 ± 19 ($P=0.77$) and 70 ± 21 ($P=0.86$) 1 and 3 months later and to 66 ± 23 before the first reinjection ($P=0.8$), respectively (Fig. 2a).

Visual acuity improved from before the first dexamethasone implantation to 1 month after the last dexamethasone implantation by 5.6 ± 1 (group 1) and 2.7 ± 3.8 letters (group 2) without achieving statistical significance (Fig. 2b). Interestingly, in group 1, the letter count increased already 7.0 letters after the first dexamethasone implantation ($P=0.04$), whereas in group 2, there was no significant increase in letter count after the first dexamethasone implantation (Fig. 2b).

Before the initial injection of dexamethasone, the mean CRT was 534 ± 208 and 529 ± 215 μm (groups 1 and 2; respectively). The value dropped to 283 ± 104 μm (group 1) and 335 ± 71 μm (group 2) by the 1-month follow-up and to 287 ± 115 μm (group 1) and 371 ± 77 μm (group 2) by the 3-month follow-up ($P=0.00000006$ and 0.00000004, group 1; and $P=0.02$ and 0.04, group 2; respectively) before increasing again to 460 ± 192 (group 1) and 547 ± 175 (group 2) μm by the time of the first reinjection ($P=0.14$ and $P=0.82$; groups 1 and 2; respectively) and decreasing once more substantially after each reimplantation (Fig. 3a). We did not observe an increase of CRT over time before each dexamethasone implantation indicating that there was no rebound phenomenon (Fig. 3b).

The post-treatment rise in IOP peaked 4 and 12 weeks after each injection of dexamethasone in group 1, whereas there was no significant change in IOP in group 2. The mean value rose from 13.4 ± 3.8 (group 1) and 14.8 ± 2.8 mmHg (group 2) at the baseline level to one of 17.2 ± 5.4 (group 1) and 16.5 ± 5.6 mmHg (group 2) and 17 ± 5.6 (group 1) and 16.1 ± 3.9 mmHg (group 2) at the 1- and 3-month follow-ups (group 1, $P=0.002$ and $P=0.004$; and group 2, $P=0.34$ and $P=0.35$; respectively) and plateaued at a level of 14 ± 2.9 (group 1) and 15.2 ± 5.9 (group 2) mmHg by the time of the

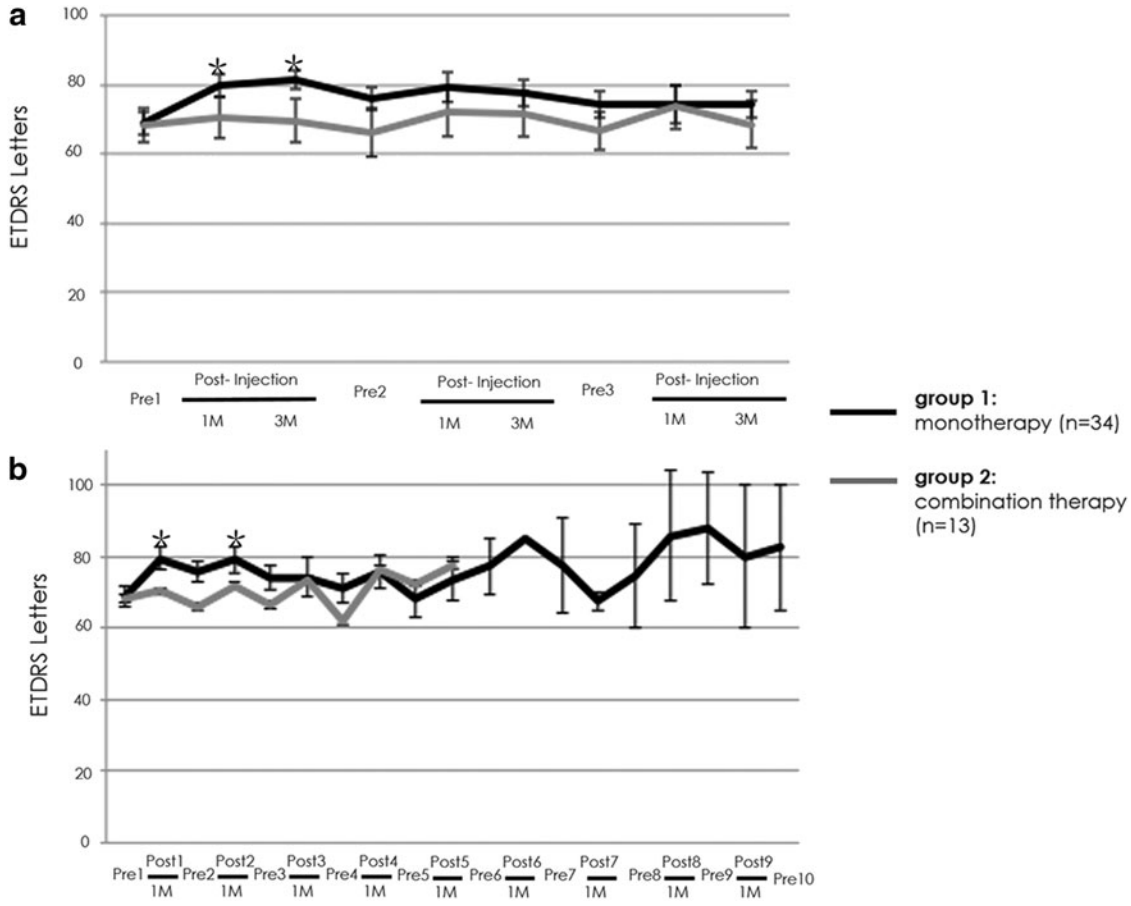

FIG. 2. Best-corrected visual acuity in ETDRS letters: **(a).** before the first injection of dexamethasone (Pre1) and 1 and 3 months later, before the second injection (Pre2) and 1 and 3 months later, and before the third injection (Pre3) and 1 and 3 months later. **(b).** Change in ETDRS letters before and 1 month after each Ozurdex implantation per eye until the 10th implantation. *Black line*: group 1 ($n=34$ eyes in 28 patients); *gray line*: group 2 ($n=13$ eyes in 10 patients); $*P \leq 0.05$. Error bars represent the SEM.

first reinjection [$P=0.48$, group 1; and $P=0.85$, group 2 (Fig. 4)].

In 2 vitrectomized eyes, a leakage from the injection site resulted in hypotony, requiring an injection of air to restore a normal IOP level. Rises of IOP were medically controlled by the administration of no more than 2 antiglaucoma agents; in group one—11 of the 34 eyes, and in group two—4 of the 13 eyes. No other unexpected adverse events were recorded.

Discussion

Our retrospective analysis revealed that dexamethasone implants improved functional and anatomic outcomes in the group of eyes that were difficult to handle under prior anti-VEGF injections with chronic DME. The effect on BCVA improvement and reduction in CRT lasted on average 4.8 ± 2.1 months before retreatment with any intravitreal agent application on a PRN basis. This is well in accordance with data from other series.[14]

Moreover, our series indicates that intravitreal injections of dexamethasone can be repeated over periods of 6–48 months without evident loss of efficacy and without induction of any unexpected side effects, which have been reported to occur to a relevant degree after treatment with triamcinolone.[2,15] Eyes requiring frequent anti-VEGF re-injections or eyes showing no complete resolution of DME with prolonged anti-VEGF treatment may be most suitable to a steroid-based treatment option.[15–19] Whether the successful outcomes reported herein can be sustained for longer periods—in our series, up to 4 years and up to 25 injections (over 20 injections >3 years: $n=2$; between 10 and 20 injections >3 years: $n=2$; between 5 and 10 injections >2 years: $n=12$; 2–5 injections >1 year: $n=18$; group 1 monotherapy)—deserves to be addressed in larger series since it would obviously contribute to better visual-adjusted quality-of-life scores.[12] The Reldex study showed favorable 3-year outcomes of dexamethasone therapy, also in treatment-naïve eyes with DME.[20]

That vitrectomized and nonvitrectomized eyes responded similarly to the intravitreal administration of dexamethasone accords with data that have been gleaned from other studies, also involving larger numbers of patients.[15,21,22] A recent study by Shah et al. reported good short-term efficacy of intravitreal dexamethasone implants in vitrectomized eyes with persistent DME and prior anti-VEGF treatment.[23] Our long-term results add to the short-time outcomes from Shah et al.'s study.

Pseudophakic eyes have been reported to respond well to intravitreal injections of dexamethasone.[24] In our study, all but 9 eyes in group 1 (26.5%) and 1 eye in group 2 (7.7%)

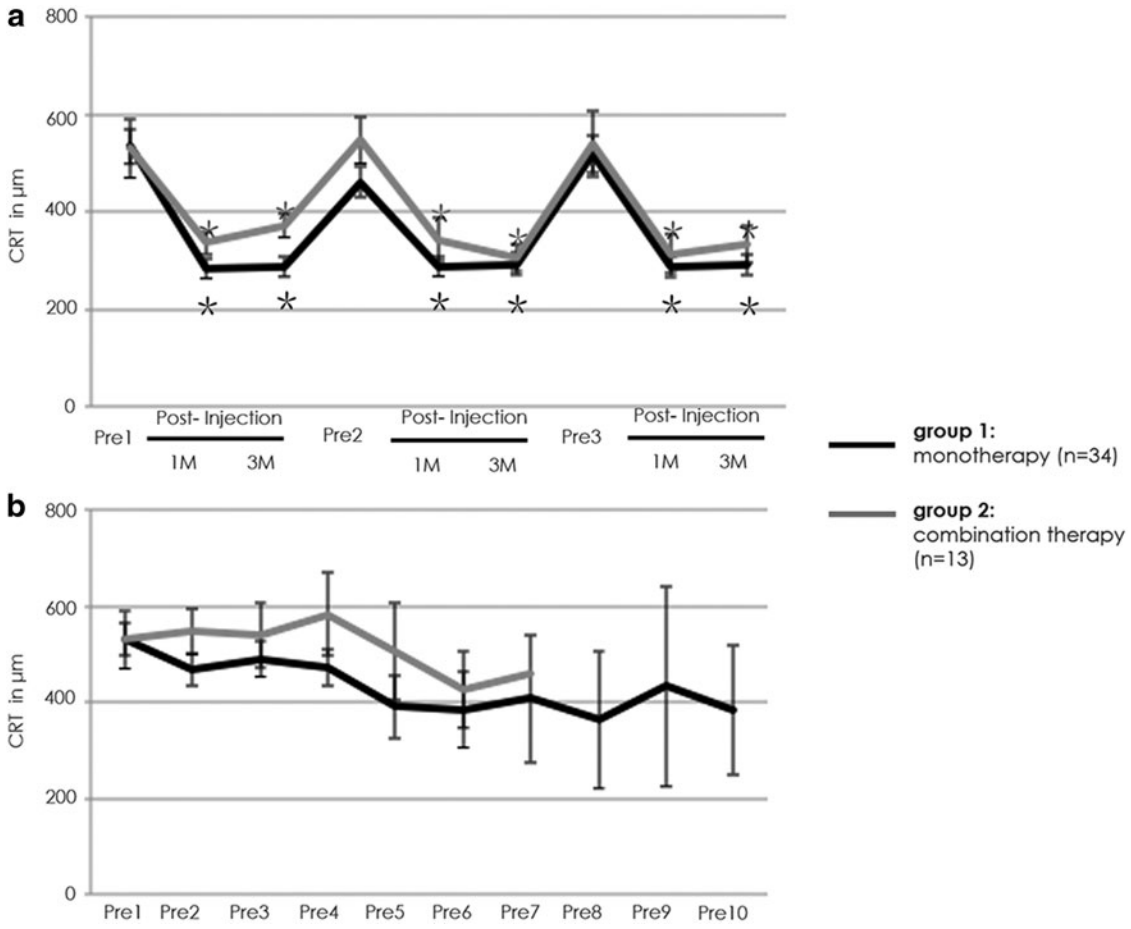

FIG. 3. Central retinal thickness (CRT) in micrometers: **(a)** before the first injection of dexamethasone (Pre1) and 1 and 3 months later, before the second injection and 1 and 3 months later, and before the third injection and 1 and 3 months later. **(b)** Change in CRT before each Ozurdex implantation per eye until the 10th implantation. *Black line*: group 1 ($n = 34$ eyes in 28 patients); *gray line*: group 2 ($n = 13$ eyes in 10 patients); $^*P \leq 0.05$. Error bars represent the SEM.

were pseudophakic. The eyes with cataract had undergone surgery during the study period, which has been shown not to modify the outcomes.[25]

A recent study by Matonti et al. and a study by Scaramuzzi et al. investigated the effect of repeated dexamethasone implant injections in DME-afflicted eyes and showed similar outcomes as our study regarding injection intervals, functional and anatomic improvement, and adverse events.[26,27]

We included only eyes with long-standing and pretreated macular edema after failure of anti-VEGF drugs. Gutiérrez-

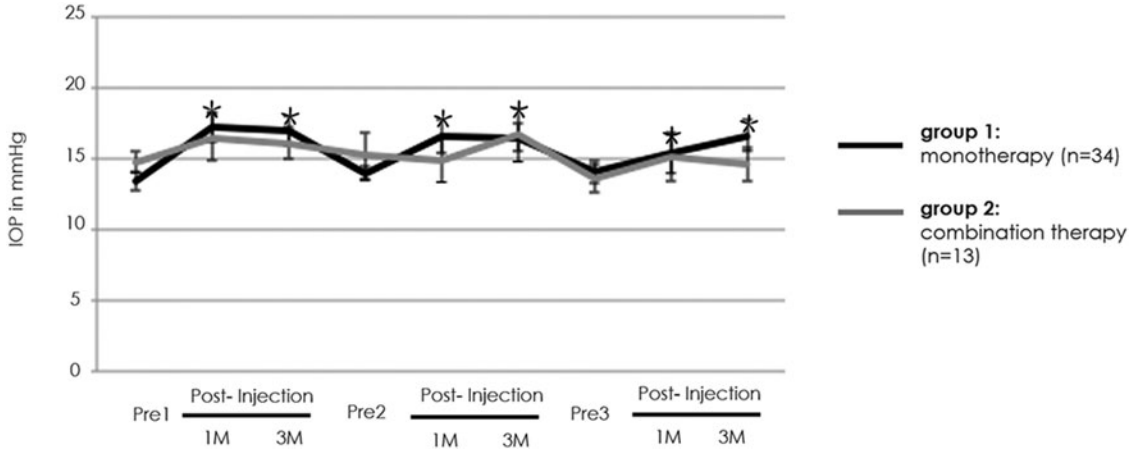

FIG. 4. Intraocular pressure (IOP) in mm of mercury (mmHg): before the first injection of dexamethasone (Pre 1) and 1 and 3 months later, before the second injection (Pre2) and 1 and 3 months later, and before the third injection and 1 and 3 months later. *Black line*: group 1 ($n = 34$ eyes in 28 patients); *gray line*: group 2 ($n = 13$ eyes in 10 patients); $^*P \leq 0.05$. Error bars represent the SEM.

Benitez et al. report outcomes in DME refractory to prior treatment that are in line with ours, but after a follow-up of only 7.6 months.[28] Pacella et al. also describe good outcomes of dexamethasone implants in eyes with DME that are refractory to prior anti-VEGF therapy over a follow-up period of 18 months.[29]

A longer period from the last anti-VEGF injection in group 1 compared with group 2 (4.8 vs. 3.7 months before switching) may explain the good early anatomic and functional results under dexamethasone monotherapy compared with group 2 eyes that received adjunctively anti-VEGF, resulting in a significant reduction in CRT, but not in visual improvement after the first dexamethasone implantation. Twelve of 13 eyes in group 2 never achieved a complete resolution of intraretinal fluid.

In conclusion, our data have revealed dexamethasone to be an efficacious and safe option in the long-term treatment of long-standing DME in eyes that have shown unsatisfactory response to other prior therapeutic regimes or require frequent injections.

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Author Disclosure Statement

J.G.G. acts as an advisor to several pharmaceutical companies and contributes to several clinical studies. The research foundation at the City Hospital Triemli has received research grants (Novartis, Bayer) and reimbursement for consultancy work of S.M. (Novartis, Bayer, Allergan, Roche, Pfenex, Clanotech). Nevertheless, neither of them nor the other authors received direct support for this study or have conflicting interests with the data that are presented in this report. Financial disclosures: S.Z. none, T.L. none, F.F. none, M.P. none, I.B.P. none, C.G. none, S.M. none, L.K. none, and J.G.G. none. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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