The Short-Term Efficacy and Safety of Dexamethasone Implant in a Difficult-to-Treat Patient Population With Persistent Diabetic Macular Edema

Deksametazon İmplantın Zor Tedavi Edilen Bir Hasta Grubu Olan Dirençli Diabetik Makula Ödemi Olgularında Kısa Dönem Etkinlik ve Güvenirliğinin Değerlendirilmesi

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ABSTRACT

Purpose: To assess the short-term safety and efficacy of intravitreal dexamethasone implant (DEX implant) in patients with persistent diabetic macular edema.

Materials and Methods: A retrospective study was conducted 24 eyes of 19 patients with persistent diabetic macular edema (≥250 µm) though macular laser and antivegf agents. Best corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure(IOP), adverse events and morphological changes on OCT were examined at baseline, month 1, 3 and 4.

Results: Preoperative mean BCVA was 0.80±0.40 (logMAR) and significantly improved 1 (0.59±0.30) and 3 months (0.64±0.35) after injection (p<0.001). Preoperative mean CMT was 586±203µm and decreased to 230±77 and 274±115 1 and 3 months after injection (p<0.001), respectively. Mean BCVA and CMT values were also similarly improved for the 4 month follow-up. Reinjection required after 3 months in 63% and after 4 months in 88% of patients. No serious adverse events were observed. 21 % of patients only had a preserved ellipsoid zone.

Conclusion: DEX implant seems to be an effective and safe treatment in patients with persistent diabetic macular edema. However, drug effectiveness is short and ellipsoid zone loss seems to be the main problem that limits the success of treatment in this difficult-to-treat patient population

Keywords: dexamethasone, macular edema, retina

ÖZ

Amaç: Persistan diabetik makula ödemi olan hastalarda intravitreal Deksametazon implantın (DEX implant) kısa dönem etkinlik ve güvenirliğinin değerlendirilmesi

Gereç ve Yöntemler: Retrospektif bu çalışmada uygulanan maküler lazer ve anti-VEGF ajanlara rağmen makula ödemi devam eden(≥250 µm) 19 hastanın 24 gözü değerlendirildi. En iyi düzeltilmiş görme keskinliği (EİDGK), santral makula kalınlığı(SMK), göz içi basıncı(GİB), yan etkiler, OCT'deki morfolojik değişiklikler başlangıçta, 1, 3, 4.aylarda değerlendirildi.

Bulgular: Enjeksiyon öncesi ortalama EİDGK 0.80±0.40 (logMAR)'dan 1. ve 3. aylarda sırasıyla 0.59±0.30 ve 0.64±0.35 logMAR'a yükseldi (p<0.001). Enjeksiyon öncesi ortalama SMK 586±203 µm iken 1. ayda 230±77 µm 3. ayda ise 274±115 µm'a düşmüştür (p<0.001). Ortalama EİDGK ve SMK 4. ay takip hastalarında da benzer şekilde düzelme gösterdi. %63 hastada 3.ay sonunda reenjeksiyon gerekirken, %88 hastada ise 4.ay sonunda enjeksiyon gerekmiştir. Hiçbir hastada ciddi bir yan etki izlenmemiştir. Sadece %21 hastada ellipsoid zonun sağlam olduğu gözlenmiştir.

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Sonuç: DEX implant persistan diabetik makula ödemi olan hastalarda etkili ve güvenli bir tedavi olarak gözükmektedir. Ancak bu zor tedavi edilen hasta grubunda ilacın etkinliği kısadır ve ellipsoid zon hasarı tedavinin etkinliğini kısıtlayan en önemli etmendir.

Anahtar kelimeler: Deksametazon, maküler ödem, retina

INTRODUCTION

Diabetic retinopathy is one of the common complications of diabetes and represents the leading cause of blindness among adults of working age in the developed world.[1] Diabetes-related central vision loss can arise either from macular ischemia or from microvascular leakage due to breakdown of the inner blood–retinal barrier (BRB), leading to macular edema.[2,3] Diabetic macular edema (DME) has been shown to be low grade inflammation process in which numerous inflammatory cells, mediators and cytokines are involved and subsequently lead to increase in vascular permeability.[4,5]

An important prospective randomized study (by the Early Treatment Diabetic Retinopathy Study –ETDRS- group) revealed that grid macular photocoagulation decreased the risk of moderate to severe vision loss from DME by 50% compared to untreated controls over 3 years.[6] This was the standard of care for over 2 decades. However, some patients can be refractory to laser treatment and this type of therapy is associated with mild visual loss, a diminished visual field, and reduced color vision and contrast sensitivity.[7,8]

An anti-VEGF agent, ranibizumab approved as a medical treatment choice due to significant long term outcomes of the phase 3 trials: RISE and RIDE; [9] compared to sham treatment, monthly injections of ranibizumab achieved a 2 to 3 fold increase in the percentage of patients who met visual improvement endpoints. However, all patients may not always respond to intravitreal anti-VEGF treatment properly. Steroids are alternative leading to reduce inflammatory mediators through a more widespread action that blocks inflammatory cytokines, prostaglandins and VEGFs.

Corticosteroids were the first pharmacologic intravitreal treatment to be used for DME. Corticosteroids have been included in the treatment of diabetic retinopathy and DME because of their anti-inflammatory and antiangiogenic effects. Intravitreal triamcinolone acetonide (TA) was more effective than placebo in improving vision in patients with refractory DME as an off label treatment.[10] Intravitreal TA or ranibizumab in combination with laser treatment showed similar efficacy in pseudophakic eyes in which there is no confounding of cataract development associated with corticosteroid in the The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study.[11]

Numerous intravitreal biodegradable and nondegradable steroid releasing implants have been designed to provide long-term drug delivery to the macular region. DEX implant, which contains micronized preservative-free dexamethasone 0.7 mg in a biodegradable copolymer of polylactic-co-glycolic acid breaking down into carbon dioxide and water in time, is designed to deliver drug to the retina over a period of up to 6 months. Intermittent release helps prevent the peak vitreous drug concentrations and frequent repeat injections, thus the implant may potentially reduce the risk of unwanted steroid-related ocular side effects (cataract formation, IOP elevation, and glaucoma) and injection-related complications (lens injury, retinal detachment, and endophthalmitis). It has been approved for use in the treatment of macular edema secondary to retinal vein occlusion, noninfectious posterior uveitis, and also DME.

The purpose of this study was to evaluate anatomical and functional outcomes of intravitreal DEX implant in patients with persistent diabetic macular edema.

MATERIALS AND METHODS

In this retrospective study we have evaluated 24 eyes of 19 patients with persistent DME. Inclusion criteria were age over 18 years, the presence of persistent DME (involving the central macula). Persistent diabetic macular edema was defined as macular edema with central macular thickness ≥250 μm by spectral domain optical coherence tomography (SD-OCT) lasting for at least 90 days after macular laser (focal/grid) and at least 3 intravitreal injections of antivegf agents (ranibizumab or bevacizumab). The exclusion criteria were ischemic maculopathy, corticosteroid responders, history or presence of other maculopathies/retinopathies (e.g retinal vein occlusion, age-related macular degeneration, üveitis) and visually significant media opacities (e. g cataract or corneal opacity), intravitreal antivegf <1 month before the DEX implant injection, macular fotocoagulation <3 months before the DEX implant injection. Patients with controlled glaucoma and epiretinal membrane with foveal depression were not excluded.

All patients included in the study underwent a complete ophtalmic examination: BCVA was assessed either using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a distance of 4 m or with Snellen charts. Anterior segment and fundus examination, intraocular pressure (IOP) measurement were performed. The presence of macular ischemia was evaluated by fluorescein angiography. Macular OCT scan was performed by Topcon 3D OCT-2000 System and CMT measurements were obtained. Postoperative morphological changes as regression of *macrocyst* (cyst with diameter >400 μ), regression of *submacular detachment* (SMD), the integrity of *ellipsoid zone* (EZ), *epiretinal membrane* (ERM) , subfoveal *retina pigment epithelium(RPE) changes* as atrophy or hipertrophy and *foveal atrophy* were

evaluated by two retina specialist. All examinations were performed at baseline, 1 and 3 months after DEX implantation. Nine patients who did not receive any treatment at month 3 were reevaluated at month 4. Recurrence criterion was fluid on OCT with at least 3 month intervals for DEX implant. HbA1c values of all patients were recorded. The main outcomes were the mean changes in BCVA (logMAR), CMT, IOP and the changes of the morphology on OCT from baseline to 1, 3 and 4 months after DEX injection.

All patients underwent DEX implant injection in the operating room under the topical anesthesia. They received topical moxifloxacin eyedrops four times for one week after injection and were examined on post-operative day 1 for visual acuity, anterior chamber reaction, intraocular pressure (IOP), and fundus evaluation by indirect ophthalmoscopy.

Informed consent was obtained from all patients before injection. This study was approved by the Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Wilcoxon tests were used to measure mean differences between pre- and post-implant values of all the parameters evaluated (BCVA, CMT, IOP) and obtained at different temporal follow-up points and also Mann-Whitney-U test was used to evaluate any correlation between EZ integrity and BCVA. A P<0.05 was considered as a significant clinical result.

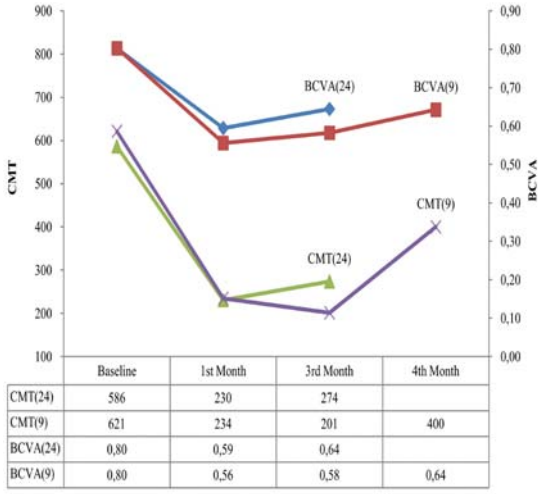
RESULTS

Twenty four eyes of 19 patients (12 men) were studied. The mean age was 61.9±9.3 years (46-79), all of them had type 2 diabetes. The mean baseline HbA1c was 7.7±1.1% (6.5-9.8). The mean number of previously performed intravitreal anti-VEGF injections was 5.2±1.9 (3-9). Eight eyes were pseudophakic and rest of them were phakic. Sixteen eyes had underwent laser photocoagulation of ischemic retina (panretinal or sectorial). All of them had underwent macular photocoagulation (grid and/or focal. Mean duration of DME was 30.3±18 months (range, 12-60 months). Baseline characteristics of the study population are summarized in **Table 1.**

A statistically significant difference was observed in BCVA, CMT at month 1, 3 and 4 compared to baseline. Preoperative mean CMT was 586±203µm and decreased to 230±77 µm (p<0.001) and 274±115 µm (p<0.001) 1 and 3 months after injection, respectively. For 4 month follow-up preoperative mean CMT was 621±213µm and decreased to 234±72 (p=0.008), 201±63 (p=0.008) and 400±202 (p=0.011) 1, 3, and 4 months after injection. In accordance with the OCT changes preoperative mean BCVA was 0.80±0.40 (logMAR) and improved to 0.59±0.30 (p<0.001) and 0.64±0.35 (p<0.001) 1 and 3 months after injection. Mean BCVA for 4 month follow-up was 0.80±0.50 (logMAR) and improved to 0.56±0.32 (p=0.007), 0.58±0.41 (p=0.008) and 0.64±0.45 (p=0.007) 1, 3 and 4 months after injection **(Table 2)**. Most of the patients (63%) had recurrence at month 3 and reinjection required with CMT ranged from 232 µm to 689 µm. 25% of patients who had better results both functional and anatomical at month 3 also had recurrences at month 4 (despite having significantly better results than baseline) and re-injection required **(Fig.1)**. IOP increased statistically significant at 1 and 3 months compared to baseline and measured higher than 25 mmHg in six eyes were well-controlled with topical antiglaucoma therapy (the maximum value was 29 mmHg at month 1) but one patient developed secondary

Tablo 1: *Baseline Characteristics and Medical History of the Study Population*

Characteristics	**n**
Patients	19
Sex Male Female	 12 7
Age, Years Mean Range	 61.9±9.3 46-79
Study Eyes (R/L)	24 (10/14)
Mean HbA1C (%)	7.7±1.1 (6.5-9.8)
Total anti-VEGF injection	5,2±1.9 (3-9)
Duration of DME (months)	30,3±18 (12-60)
Lens status Phakic Pseudophakic	 16 8
Previous sectorial or panretinal photocoagulation	16



	Baseline	1st Month	3rd Month	4th Month
CMT(24)	586	230	274	
CMT(9)	621	234	201	400
BCVA(24)	0,80	0,59	0,64	
BCVA(9)	0,80	0,56	0,58	0,64

Fig 1 Quantitative analysis of the mean BCVA and CMT values for all patients (n=24) and separately for 4 month follow ups (n=9). Peak imporovements are observed between months 1 and 3. Both BCVA and CMT increases after recurrences but the latter is obviously faster.

Tablo 2: *Baseline demographics and visual and anatomical results after Dex implant*

Eye no.	Age	Sex	OD/ OS	BCVA				CMT			
				BL	M1	M3	M4	BL	M1	M3	M4
1.1	65	F	OD	0.90	0.76	0.78		380	314	393	
2.1	67	F	OD	1.80	1.08	1.28	1.40	925	171	119	826
2.2	67	F	OS	1.04	0.80	0.80	1.00	685	210	127	537
3.1	67	F	OD	0.78	0.74	0.70		704	406	689	
4.1	60	M	OD	0.74	0.74	0.74		392	177	232	
4.2	60	M	OS	0.92	0.80	0.68		890	173	257	
5.1	67	M	OS	0.60	0.26	0.20	0.20	576	268	257	250
6.1	49	M	OD	0.32	0.32	0.22	0.20	457	356	212	189
6.2	49	M	OS	0.24	0.14	0.10	0.20	435	283	314	438
7.1	59	M	OD	1.10	0.84	0.94	1.00	820	304	199	398
8.1	65	M	OS	0.30	0.20	0.20		548	312	252	
9.1	79	F	OS	0.90	0.40	0.50		351	241	273	
10.1	47	M	OS	0.92	0.74	0.72		712	267	329	
11.1	55	M	OS	0.54	0.40	0.60		680	333	411	
12.1	63	F	OS	1.84	1.34	1.60		811	124	309	
13.1	46	F	OS	0.50	0.40	0.50		665	171	234	
14.1	74	M	OD	1.00	0.70	0.76	0.80	832	154	184	420
15.1	63	M	OS	0.30	0.26	0.26	0.26	280	149	160	161
16.1	69	M	OS	0.36	0.20	0.24		454	176	215	
17.1	52	M	OD	1.20	0.90	0.98		782	140	339	
17.2	52	M	OS	0.70	0.60	0.74		251	174	229	
18.1	74	F	OD	0.58	0.44	0.60		304	220	316	
18.2	74	F	OS	1.04	0.60	0.64		548	187	277	
19.1	62	M	OD	0.82	0.60	0.68	0.72	580	215	238	380

OD: Right Eye. OS: Left Eye. BL: Baseline. M: Month

glaucoma in both eyes. There was no endophthalmitis or inflammatory reaction during follow up.

The morphological changes on Optical Coherence Tomography

Six eyes which had submacular detachment at baseline (25%) had dramatic decreases in fluid heights at month 1 and complete resolution at month 3. 12 eyes had macrocyst at baseline (50%) with mean thickness of 586 µm (range 434-878). All macrocysts completely regressed at month 1. The formation of the macrocyst and SMD decreased apparently compared to baseline for the next recurrences.(**Fig.2**) Intact EZ were observed after regression of edema in only 21% of patients and loss of EZ were significantly related to poor visual outcome **(Table 3.)** 42% of patients had marked foveal atrophy**.** Patients with visible ERM (21 %) also had decreases in fluid heights and increases in visual acuity. There were subfoveal RPE changes as atrophy or hipertrophy on OCT accompanying EZ defects in 7 eyes **(Fig.3)**.

Tablo 3: *Correlation between EZ integrity and BCVA*

Mean BCVA (logMAR	Baseline	1st Month	3rd Month
EZ intact	0.4±0.2	0.2±0.1	0.2±0.1
EZ loss	0.9±0.4	0.7±0.3	0.8±0.3
p value*	0.013	0.002	0.002

*Mann-Whitney U test

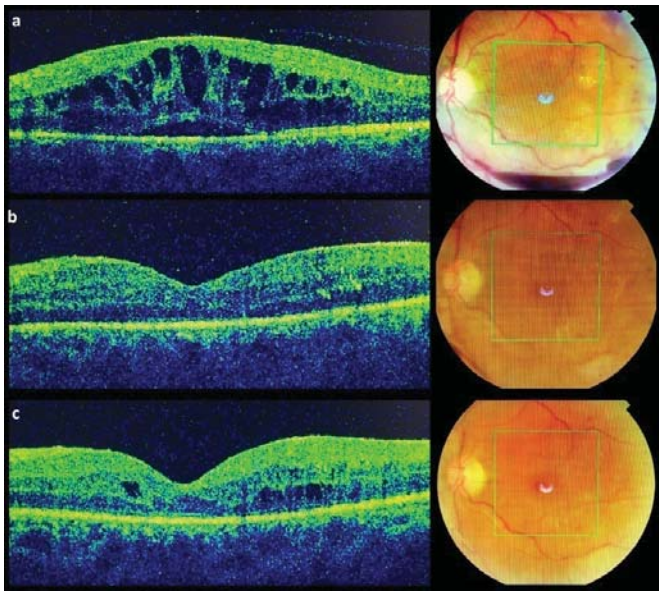


Fig 2 *Good anatomical and visual response to Dex implant in a resistant DME case. a. Representative case showing macrocysts and SMD on OCT at baseline following 4 ranibizumab injections and macular laser (VA:0.90 logMAR). b. The cysts and SMD completely disappeared after a single Dex implant injection at month 1 (VA:0.70 logMAR). c. There are intraretinal cysts at month 3 visible on OCT but visual acuity remains stable (VA:0.70 logMAR). Proliferative changes have also been improved after Dex implant seen in colour fundus photographs. DME: Diabetic macular edema. SMD: serous macular detachment. OCT: Optical coherence tomography. VA: Visual acuity.*

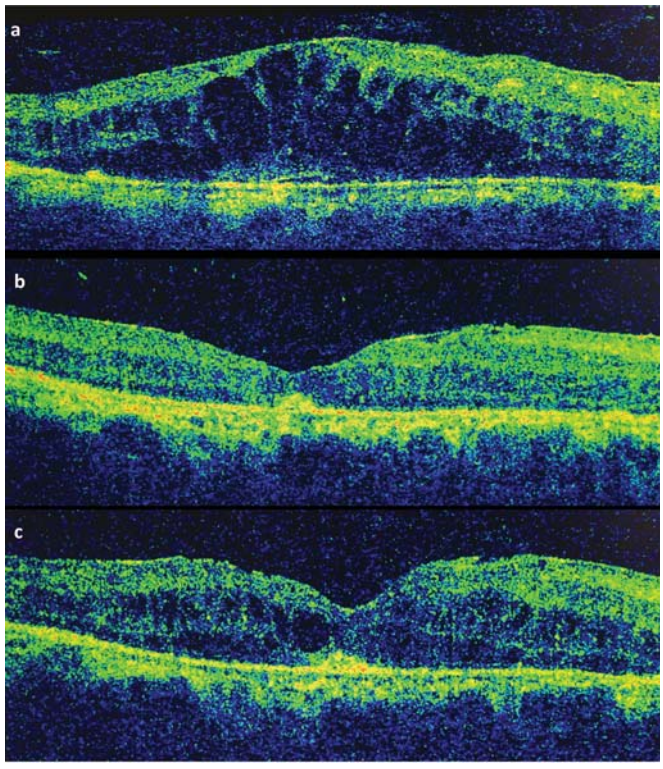


Fig 3 *The response of chronic DME to Dex implant in an atrophic case. a. Macrocysts, SMD and ERM are observed on OCT following 5 ranibizumab injections and macular laser at baseline (VA:1.20 logMAR). b. The cysts and SMD completely disappeared after a single Dex injection at month (VA:0.90 logMAR) but EZ loss and RPE changes are seen representing the chronicity of the edema. c. The microcysts are present at month 3 on OCT again (VA:0.98 logMAR). ERM: Epiretinal membrane. EZ: Ellipsoid zone. RPE: Retina pigment epithelium.*

DISCUSSION

Phase II and Phase III studies have assessed the efficacy of DEX implant (0.7 mg or 0.35 mg) in improving function and anatomic outcomes in patients with DME.[12-14] Although naive patients were also considered, patients with refractory diabetic edema were dominant in similar studies and DEX implant seems to be a good treatment option for both groups.[13-17] There was no naive patient in our study and there was no limit for baseline BCVA (range: counting fingers-43 letters ETDRS) differently from many previous clinical studies with lower limit sets for BCVA.

Previous clinical studies have shown that the efficacy of DEX implant declined rapidly from the 4th month in the refractory DME.[15,17] In our study, the reinjection interval was compatible with the literature but shorter. Reinjection required after 3 months in 63% and after 4 months in 88% of patients. The long duration of edema (mean 30.3±18), the poor response to previous treatments and the high level of HbA1c are probable risk factors for shorter retreatment interval in our study. OCT was used as reinjection criterion in order to keep retina dry as far as possible in this difficult-to-treat patient population with damaged retina by long term presence of fluid. The values of BCVA were considerably better than baseline except 5 eye in time of reinjections. These results were in accordance with Bonnin et al. BCVA gains were consistent until 4th month despite recurrences of edema in most cases.[18]

We also analyzed the morphological findings on OCT. It is known that the treatment of the DME make submacular detachment regressed.[19] DEX implant was considerably effective in regression of all fluids and also macrocysts which could be the marker of the degenerative changes due to long term presence of fluid. Turgut and et al. demonstrated a relationship between HbA1c level and SMD, and it is related to RPE damage because of bad regulation and chronic course of diabetes.[20] The rate of SMD reported in the previous studies is variable based on resolution of the OCT devices. We used Topcon 3D OCT-2000 System and rate was 25% at baseline. Dramatic decreases in fluid heights at month 1 and complete resolution at month 3 were observed despite relatively high level of HbA1c. The formation of the macrocyst and SMD also decreased apparently compared to baseline for the next recurrences. The ellipsoid zone which was previously indicated as the photoreceptor inner segment/outer segment (IS/OS) junction, is now claimed to be formed essentially by

mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors. The distance from the EZ line to the ELM is shorter than that from the EZ line to the RPE in a normal fovea. In this study, an intact EZ was observed after regression of edema only in 21% of the patients, also foveal atrophy was common. It is well-known EZ integrity is a good indicator of photoreceptor function, as it correlates with changes in visual acuity independent of retinal thickness[21]. Hence, EZ loss seems to be the main problem that limits the success of treatment in this difficult-to-treat patient population. Chronicity of edema may lead to RPE changes overlooked on fundus examination but can be revealed clearly on OCT. They seemed to be hiperreflective foci underneath the fovea accompanying EZ defects and also were argued to be a prognostic factor like EZ. This has also been demonstrated in long-term follow up in patients who were treated with ranibizumab for retinal vein occlusion by Farinha and et al. They found that baseline BCVA and disruption of the RPE were predictors of final BCVA.[22] There were subfoveal RPE changes as atrophy or hipertrophy on OCT in 7 eyes in the current report. The contribution of the other morphological changes are unclear in prognosis but obviously atrophic changes accompanied EZ loss. The patients with vitreoretinal interface abnormality like ERM was excluded in most previous studies, complete or partial regression of fluid and increase in BCVA were observed in 5 patients with ERM in our study. Because microvascular leakage and traction forces are both responsible for fluid accumulation in these patients.

Common complications of ocular corticosteroid therapy are IOP elevation and cataract formation/progression. Dexamethasone is less lipophilic than fluocinolone acetonide and shows less sequestration in the lens and trabecular meshwork[23] and so it is thought that DEX implant has potentially lower risk of causing IOP elevation and cataract. The IOP levels reached a peak at approximately 6 weeks after each DEX implant injection and returned to baseline levels within 6 months postinjection. In accordance with previous studies, statistically significant IOP increases observed at 1 and 3 months after injection and six eyes with IOP higher than 25 mmHg (the maximum value was 29 mm Hg at month 1) were treated and well controlled with topical antiglaucoma therapy. IOP elevation was permanent in two eyes of one patient within 9 months. In Geneva study[24] 29.8% cataract progression was observed in patients that received 2 DEX implant 0.7 mg injections versus 5.7% in sham-treated phakic eyes over 12 months; cataract surgery was performed in 1.3% DEX treated and 1.1% sham-treated eyes. However in Mead study[13] there was a 60% rate of cristalline lens surgery at 3 years. It is difficult to comment cataract surgery rate performing only one DEX implant, whereas cataract development is associated with cumulative dose.

DEX implant is generally used as a terminal stage treatment. However Mozart study[25] implied that previous treatments were negative factors of recovery and also Barranco et al. found that results were also more succesful in naive patients.[26] In our cohort, patients had edema periods 1 to 5 years. 16 of 24 eyes received laser photocoagulation (panretinal or sectorial) and all of them received focal/grid macular laser which were considered as negative factors. Therefore, we believe that better results could be achieved both functionally and anatomically if DEX implant was used at an earlier stage. There is a need for further studies using implant as a primary or earlier stage treatment.

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