Efficacy of Dexamethasone Implant versus Intravitreal Ranibizumab Treatment for Chronic Diabetic Macular Edema in Patients with Type 2 Diabetes Mellitus

Tip 2 Diyabetik Hastalarda Kronik Diyabetik Makula Ödem Tedavisinde Deksametazon İmplant ve İntravitreal Ranibizumab'ın Etkinliğinin Karşılaştırılması

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ABSTRACT

Purpose: To evaluate the efficacy of an intravitreal dexamethasone (DEX) implant versus intravitreal ranibizumab (RAN) for chronic diabetic macular edema (DME) in patients with type 2 diabetes mellitus.

Materials and Methods: In this retrospective, comparative, cohort study, 28 eyes of 22 patients received DEX implant at every 24 weeks. Thirty-seven eyes of 30 patients received RAN injections on pro re nata (PRN), immediately after three loading doses. Main outcome measures included best-corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP) and incidence of side effects in both groups.

Results: The mean BCVA change was -0,11 Log MAR in DEX group and -0,55 Log MAR in RAN group at month 12. There was a significant difference in BCVA between the DEX group and RAN group at months 6 and 12 (p =0.0001 and p=0.0001). Mean CMT was significantly decreased in both groups from the baseline to months 6 and 12 (DEX: p=0.001 and p=0.0001, RAN: p=0.0001, p=0.0001). Mean CMT changes for 6 months and 12 months were -80 µm and -127 µm in the DEX group, and -204 µm and -227µm in the RAN group. Mean IOP was increased remarkably in the DEX group compared to the RAN group. However, 7 eyes with IOP higher than 21 mmHg were well controlled with topical anti-glaucoma drugs in DEX group.

Conclusion: The study demonstrated that more favorable functional and anatomic outcome could be provided by RAN injection than DEX implant for 12 months. BCVA and CMT were improved significantly as soon as one month and up to 4 months in DEX implant treatment, but were not maintained as well as RAN treatment.

Key Words: Dexamethasone implant, diabetic macular edema, diabetic retinopathy, ranibizumab.

ÖZ

Amaç: Tip 2 diyabetik hastalarda kronik diyabetik makula ödemi (DMÖ) tedavisinde intravitreal ranibizumab (RAN) ile intravitreal deksametazon (DEX) implantı' nın etkinliğini değerlendirmek.

Materyal ve Metot: Bu retrospektif, karşılaştırmalı, kohort çalışmasında, 22 hastanın 28 gözüne her 24 haftada bir DEX implant ve 30 hastanın 37 gözüne, üç yükleme dozundan hemen sonra pro re nata (PRN) protokolüne uygun olarak RAN enjeksiyonu yapıldı. İki grupta, en iyi düzeltilmiş görme keskinliği (EDGK), merkezi makula kalınlığı (MMK), göz içi basıncı (GİB) değerleri ve yan etkiler açısından karşılaştırıldı.

Bulgular: On iki aylık EDGK ortalama değişimi DEX grubunda -0,11 Log MAR ve RAN grubunda -0,55 Log MAR olarak bulundu. DEX grubu ile RAN grubu arasında 6. ay ve 12. ayda EDGK'da istatistiksel olarak anlamlı fark vardı (p = 0,0001 ve p = 0,0001). Ortalama MMK, başlangıç değerlerine göre her iki grupta da 6. ay ve 12. ayda (DEX: p=0,001 ve p=0,0001, RAN: p=0,0001, p = 0,0001) anlamlı şekilde azaldı. MMK'nın 6 ay ve 12 aylık ortalama değişiklikleri -80 µm ve -127 µm idi. DEX grubu ve RAN gruplarında sırasıyla -204 µm ve -227µm ola-

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Geliş Tarihi - Received:
Kabul Tarihi - Accepted:
Ret-Vit 2019; 28: 19-25

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rak bulundu. Ortalama GİB, DEX grubunda RAN grubuna göre belirgin olarak arttı. Bununla birlikte, GİB 21 mmHg' dan yüksek olan DEX grubundaki 7 gözdeki basınç topikal anti-glokomatöz ilaçlarıyla kontrol altına alındı.

Sonuç: Bu çalışmada, 12 ay boyunca RAN enjeksiyon tedavisi ile DEX implantasyonuna göre tercihen daha iyi fonksiyonel ve anatomik sonuçlar sağlanabildiği görüldü. EDGK ve MMK da, DEX implant tedavisinde bir aydan kısa bir sürede belirgin şekilde iyileşme izlenmesine rağmen, 4 aydan sonra RAN tedavisinde olduğu gibi devamlılık sağlanamamıştır.

Anahtar Kelimeler: Dekzametazon implant, diyabetik makular ödem, diyabetik retinopati, ranizumab.

INTRODUCTION

Diabetic macular edema (DME) is one of the major causes of visual impairment in patients with diabetic retinopathy.[1,2] In Europe and the United States, 7%–12% and 1%–3% of the diabetic population suffers from visual impairment due to DME.[3]

Diabetic macular edema results from the exudation and accumulation of extracellular fluid and proteins in the macu- la due to the breakdown of the blood-retina barrier (BRB), leukocytosis and expression of inflammatory factors, such as VEGF, intercellular adhesion molecule-1, tumor necrosis factor-alpha, and interleukin-6; and alterations in endothelial tight junction proteins.[4, 5] The increased levels of inflammatory mediators results in Muller cell dysfunction owing to intracellular fluid accumulation and retinal edema. The inflammatory mediators and glutamate may lead to disruption of the inner nuclear layer and cell death.[6]

Focal and grid laser photocoagulation therapy can be applied for micro aneurysms and areas of diffuse leakage to reduce DME.[7,8] Intravitreal anti-VEGF agents are also associated to remarkable benefit in DME, as reported in long- term outcomes of RAN therapy for diabetic macular edema; as shown in two phase III trials over 36 months: RISE and RIDE[9] and a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2.[10]

Anti-VEGF agents directly inhibit the activity of vascular permeability factor (VEGF); however, corticosteroids decrease the production and release of VEGF and also pro-inflammatory cytokines, and support the barrier function of vascular tight junctions.[11,12]Intravitreal corticosteroids block the production of inflammatory mediators, such as VEGF, and inhibit leukostasis.[12,13] Dexamethasone is an anti-inflammatory agent that is more active than triamcinolone by 6-folds and cortisol by 30-folds. In 2014, a sustained-release intravitreal 0.7 mg dexamethasone delivery system was approved by Food and Drug Administration (FDA) and Commission Européenne (CE) for the treatment of DME, based on the results of MEAD study. Boyer et al. reported its efficacy and safety in the treatment of DME when delivered to the vitreous cavity by a sustained-release intravitreal implant.[14]

The aim of this study was to assess the efficacy and safety profile of an intravitreal dexamethasone (DEX) implant versus intravitreal ranibizumab (RAN) for chronic DME and to determine the long-term effects of the drugs.

MATERIALS AND METHODS

The study included NPDR or PDR patients with indication for laser photocoagulation and intravitreal RAN or DEX implant injection and underwent these treatments between January, 2013 and May, 2016. This study was approved by local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent before injection. All collected data were retrospectively evaluated.

In all patients, history was taken before procedure. All patients underwent cardiologic examination, electrocardiogram, and blood tests that included glycosylated hemoglobin (HbA1c). All patients gave written informed consent before injection. Initially, all patients included in the study underwent a complete ophthalmic examination, including BCVA (log MAR), intraocular pressure (IOP) measurement by Prismatic applanation, and fundus fluorescein angiography (FFA). Central foveal thickness (CFT) was measured by spectral domain OCT (Cirrus 4000, HD-OCT, Carl Zeiss Meditec Inc., Dublin, CA) and the presence of a retinal thickness greater than 275 mm was confirmed.

This retrospective study included all patients who had chronic DME (unilateral or bilateral) and Type 2 Diabetes Mellitus. Sixty-five eyes of 52 patients with chronic DME (over 275 micrometers) were assigned into two groups: DEX group (0.7 mg; 28 eyes of 22 patients); and RAN group (0.5 mg/0.05 ml; 37 eyes of 30 patients).

In the RAN group, monthly injections for 3 months (loading dose) followed by 0.5 mg dose PRN dosing was maintained (ranibizumab injections were given every four weeks up to week 12 and on a pro re nata (PRN or 'as needed basis'). In DEX implant group, the patients received implant on every 24 weeks.

Inclusion criteria were: age over 18 years, best-corrected visual acuity (BCVA) between 1.22 and 0.4 logarithms of the minimal angle of resolution (log MAR), and presence of chronic DME. Chronic DME is defined as DME present for a period of 6 months or more with CFT greater than 275 microns as measured by spectral-domain optical coherence tomography (SD-OCT).[9, 10, 14]

Patients were excluded if they had a history of uveitis (in either eye), history of glaucoma, evidence of either vitreo-

macular traction (in either eye) or active proliferative diabetic retinopathy (study eye), hypertension uncontrolled by medication, pregnancy, severe cataract, venous occlusions by SD-OCT, age-related macular degeneration, history of cataract surgery (within the previous six months), YAG la- ser capsulotomy (within 6 months prior to the trial), pre- vious vitrectomy, panretinal or grid laser photocoagulation (within 6 months prior to investigation), incompliance with follow-up periods. All patients were previously treated with anti-VEGF.

All the injections were given according to a standardized procedure in an operating room. DEX implant (0.7-mg implant of dexamethasone, Ozurdex; Allergan, Inc. Irvine, CA) was administered via intravitreal route through the pars plana using the original implanting device. After the administration, IOP and light perception were assessed. Complete ophthalmic examination, including IOP measurements, was performed at baseline and monthly thereafter. The main outcomes were the changes in mean BCVA, CFT, and IOP measures from baseline to follow-up visits

Statistical analysis

The examination of whether BCVA, CFT, and IOP measurements at baseline, first week, and per month satisfied the underlying assumptions of parametric statistical tests such as normality across groups and homogeneity of the group variances using Shapiro-Wilk and Levene's tests indicated that normality assumption was mostly violated by the data whereas the homogeneous group variances were present. Therefore, nonparametric statistical tests were utilized for between-groups comparisons at each time point and comparisons over time in the groups.

For inter-group comparisons, Mann-Whitney-U tests were used to compare VA, CFT, and IOP measurements at each time point between DEX implant and RAN groups. Wilcoxon tests were used to compare differences between pre- and post-injection values of all the parameters evaluated and obtained at different time points (at month 1–12) within groups as follow-up tests once a statistically significant Friedman test was obtained. Pearson's correlation coefficients were used to evaluate the linear association between BCVA and CFT. All data are descriptively presented as the mean ± standard deviation (SD) in tables. Statistical tests were evaluated at the nominal alpha levels with Bonferroni adjustment. Statistical analyses were performed using SPSS (version 18.0; SPSS Inc., Chicago, IL). All data are presented as the mean ± standard deviation (SD). A p value <0.05 was considered as statistically significant.

RESULTS

Sixty-five eyes of 52 patients with chronic DME were included and analyzed as DEX implant group (9 men, 13 women; mean age 60.67±10.17 years, range 44–82 years old) and RAN group (15 men, 15 women; mean age 58.5±12.6 years, range 41–77 years old). The duration of DM was 13.82±6.67 years (range 4-27 years) for the DEX implant group, and 12.33±5.68 years (range 4-25 years) for the RAN group. The mean HbA1c value at baseline was 7.32% ± 0.85 (range 6 - 8.6) for the DEX implant group, and 7.15%±0.90 (range 5.2- 8.9) for the RAN group. In the DEX implant group, 8 eyes had history grid laser treatment, and 7 eyes had history of scatter laser treatment. In the RAN group, 10 eyes had history grid laser treatment, and 7 eyes had history scatter laser treatment. Prior to the study, the numbers and intervals of the intravitreal RAN injections were 4.02±1.11 (range 3-7) and 1.55±0.24 (range 1, 16-2.4) in the RAN group whereas 4.03±0.099 (range 3-6) and 1.49±0.16 (range 1.13-1.75) in the DEX implant group, respectively. During the study, the numbers of the intravitreal RAN injections were 9.02±1.11 (range 8-12) in the RAN group. At baseline and follow-up period, FFA showed no cases of macular or perifoveal retinal ischemia (Table 1).

Table 1. *Demographic and clinic characteristic of DEX implant group and RAN group.*

	DEX (n=28)	RAN(n=37)	p-value
Eye (R/L)	15/13	21/16	*0.800
Age (years, mean ± SD)	58.2±13.7	60.2±8.5	*0.958
Gender (M/F)	9/13	15/15	*0.271
Phakic/Pseudophakic	23/5	31/6	*0.862
DM (years, mean ± SD)	14.71±6.27	12.27±5.90	*0.132
HbA1c (%, mean ± SD)	7.32 ±0.85	7.15±0.90	*0.399
NPDR/PDR	21/7	30/7	*0.558
Hypertension	6	7	*0.782
RAN prior to study (mean ± SD)	4.03±0.99	4.02±1.11	*0.839
RAN during study (mean ± SD)		9.02±1.11	

DM: diabetes mellitus, DME: diabetic macular edema, SD: standard deviation, RAN: ranizumab:, R:right L:left, M. male, F: female, NPDR: non-proliferative diabetic retinopathy, PDR: non-proliferative diabetic retinopathy, **Chi-square test, *Mann-Whitney U test

The mean BCVA in the DEX implant and RAN groups were 0.83±0.18 log MAR vs.0.75±0.22 log MAR at baseline, 0.56±0.13 log MAR vs. 0.69±0.23 log MAR at month 1, 0.50±0.12 log MAR vs. 0.62±0.21 log MAR at month 2, 0.55±0.12vs 0.55+0.19 at month 3, 0.61±0.12 log MAR vs. 0.52±0.20 log MAR at month 4, 0.70±0.11 log MAR vs. 0.45±0.19 log MAR at month 5, 0.74±0.13 log MAR vs. 0.42 ±0.15 log MAR at the month 6, 0.46±0.10 log MAR vs. 0.36±0.12 log MAR at month 7, 0.50±0.02 log MAR vs. 0.34±0.11 log MAR at month 8, 0.55±0.02 log MAR vs. 0.29±0.11 log MAR at month 9, 0.60±0.01 log MAR vs. 0.24±0.10 log MAR at month 10, 0.66±0.02 log MAR vs. 0.21±0.09 log MAR at month 11 and 0.69±0.02 log MAR vs. 0.20±0.08 log MAR at the month 12, respectively (Figure. 1). There was a statistically significant difference in visual acuity between the DEX implant group and RAN group in all time points other than month 3 (p= 0.578).

The mean CFT in the DEX implant and RAN groups were 524.2±143.6µm vs. 466.1±136.7 µm at baseline, 342.3±133.7 µm vs. 347.2±83.9 µm at month 1, 289.7±115.4 vs. 340.7±81, 8 µm at month 2, 275.5±87.7 µm vs.328.7±77.2 µm month 3, 267.2±62.3 vs. 244.9±29.2 at month 4, 317.3±65.4 vs. 240.2±36.1 month 5, 444.3±108.5 µm vs. 261.5±32.2 µm at month 6, 341.3±80.9 vs. 241.8±28.7 µm at month 7, 293.3±60.7 µm vs. 241.9±34.2 µm at month 8, 261.8+54.8 µm vs 250.3±29.7 µm at month 9, 256.9±56.9 µm vs. 236.6±32.8 µm at month 10, 304.7±51.7 µm vs. 240.2±40.1 µm at month 11, 397.6±44.3 µm vs. 239±33.9 µm at month 12, respectively (Figure. 1). Mean changes of CFT for 6 months and 12months were 79.9 µm and 126.6 µm with the DEX implant group, whereas 56.9 µm and 227.1 µm with the RAN group (Table 1, Figure 2). A rebound of macular edema was observed between month 5 and month 6, month 11 and month 12 in the DEX implant group (Table 1). BCVA and CFT figures had tendency as biphasic line in DEX implant group.

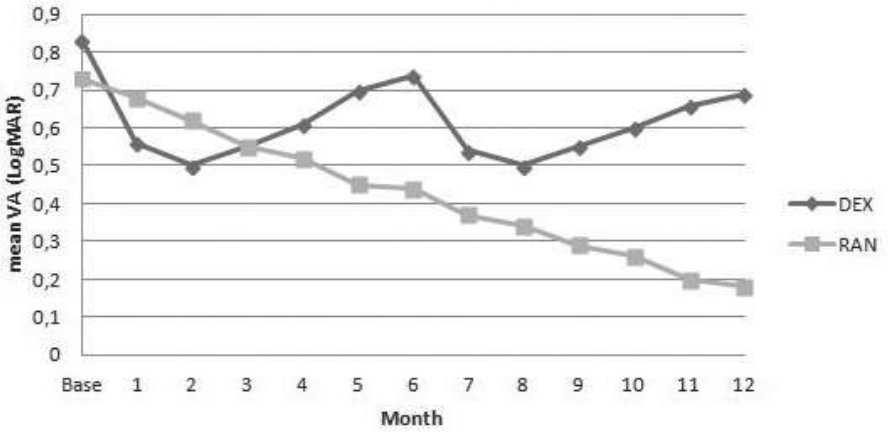

Figure 1. *Graph showing changes in mean BCVA from baseline over 12 months, during treatment with intravitreal ranibizumab (RAN) or dexamethasone implant (DEX).*

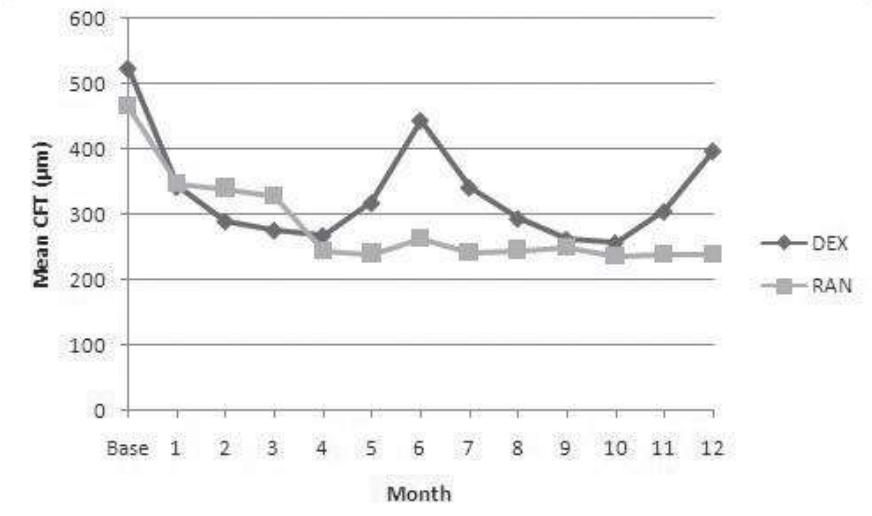

Figure 2. *Central Foveal Thickness Changes following DEX implant and intravitreal RAN.*

The mean IOP in the DEX implant and RAN groups were 14, 9±1.4 mmHg vs. 14.9±1.7 mmHg at baseline, 20.3±3.2 mmHg vs. 16.2±2.0 mmHg at month 1, 20.2±3.4 mmHg vs. 15.8±1.8 mmHg at month 2, 19.2±3.6 mmHg vs. 16.0±1.5 mmHg at month 3, 18.1±1.8 mmHg vs. 15.9±1.6 mmHg at month 4, 17.3±1.4 mmHg vs. 15.9±1.5 mmHg at month 5, 16.7±1.3 mmHg vs. 15.8±1.4 mmHg at month 6, 19.6±1.8 mmHg vs. 16.0±1.2 mmHg at month 7, 19.2±2.5 mmHg vs. 15.5±1.5 mmHg at month 8, 18.9±2.5 mmHg vs. 15.1±1.3 mmHg at month 9, 18.0±1.7 mmHg vs. 16.3±1.3 mmHg at month 10, 17.1±1.5 mmHg vs 16.0±1.3 mmHg at month 11, 16.7±1.2 mmHg vs. 15, 7±1.1 mmHg at month 12, respectively.

There was significantly increased IOP from baseline to month 12 in the DEX implant group but not increased IOP at months 6, 8, 9 and 12 in the RAN group (Figure 3). During the follow-up period, we found that IOP was higher than 21 mmHg in 7 eyes (25%) in the DEX implant group. These eyes were treated and controlled with topical anti-glaucoma therapy. Cataract formation was observed in 2 cases of DEX implant group during the follow-up. There was no inflammation, infection, thromboembolic events, ocular toxicity, or cataract progression observed in any of the patients in RAN group.

Pearson correlation showed positive relation between BCVA and CFT at month 3 in DEX implant group (p=0.389, r=-0.41), but there was no such relation in RAN group.

DISCUSSION

In this study, intravitreal RAN treatment seemed superior to DEX implant treatment in average change from baseline BCVA over 12 months in the protocol where DEX implant was ad- ministered every 6 months and RAN injections was applied on pro re nata (PRN). At the follow-up, we found that intravitreal RAN injection was highly effectively for the treatment of chronic DME. The improvement of BCVA seemed to start at the first month and reached a peak level between month 2 and month 3; then it was decreased after month 3. In the other hand, the regression of CFT was increased at the first month and reduced after month 4 and month 10. This result might be linked to reduced release of the drug rather than diabetic dysregulation since all included patients in both groups had lower than mean HbA1c values of 8.0%. However, FFA demonstrated mo ischemia during follow-up.

In clinical practice, intravitreal steroids are rarely preferred as the initial treatment due to the ocular side effects. If there is any contraindication about anti-VEGF treatment or in-compliance with patients, steroid implants can be considered for DME.

Lazic and coworkers evaluated the efficiency of intravitreal dexamethasone implant in patients with chronic DME unresponsive to three monthly 1.25 mg intravitreal bevacizumab injections and reported significant improvement in BCVA at month 2 and in CFT at month 1, 2 and 3.[15]

In the other hand, a single intravitreal Ozurdex implant could produce improvement in BCVA and CFT as soon as the first day after the injection, and such improvement was maintained until the month 4.[16]

In results of BEVORDEX study at year one, Gillies and coworkers reported that 42 eyes were randomized to receive bevacizumab every 4 weeks whereas 46 eyes were randomized to receive a dexamethasone implant every 16 weeks. The mean improvement in BCVA was 8.9 letters (95% CI, 6.27-11.6) for bevacizumab-treated eyes whereas 5.6 letters (95% CI, 0.90-10.3) for dexamethasone implant treated eyes at month 12 month. The

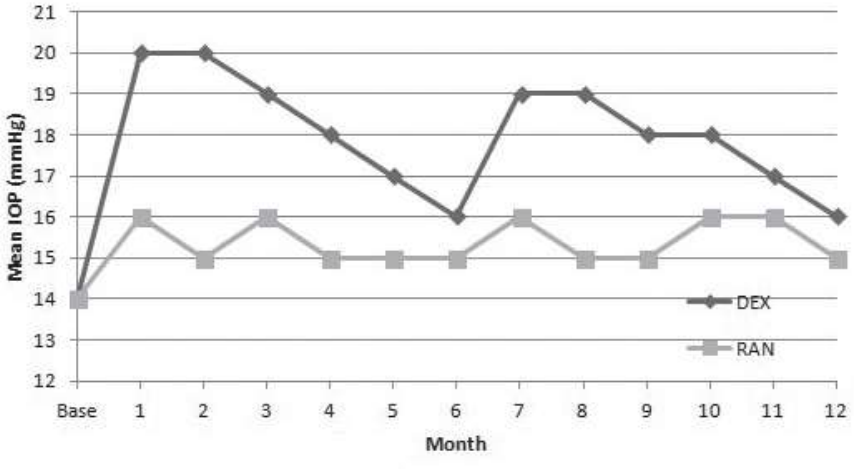

Figure 3. *Intraocular Pressure Changes following DEX implant and intravitreal RAN*

difference between two groups did not reach statistical significance (p = 0.24). Mean CFT decreased by 122 mm for bevacizumab eyes and 187 mm for dexamethasone implant eyes (p = 0.015). According to published results of the BEVORDEX study at year 2, eyes continued on the same treatment allocation. The VA improvement seen at 12 months in both group was maintained at 24 months, with 20 of 46 DEX implant-treated eyes (43%) and 19 of 42 bevacizumab-treated eyes (45%) achieving > 10 letter VA gain (p = 0.99). There was no difference between the CFT of groups at month 24.[17,18]

Maturi and coworkers found that combination therapy with bevacizumab and the dexamethasone delivery system (DDS) reduced the central retinal thickness (CRT) signifi- cantly better (−45 ±107 mm vs. −30 ± 100 mm; p = 0.03) than continued bevacizumab monotherapy while achieving similar visual outcomes (+5.4 letters vs. +4.9 letters) at year one.[19]

In their study, Totan and coworkers reported efficacy of DEX implant in patients with chronic diabetic macular edema resistant to intravitreal bevacizumab treatment where BCVA significantly (p = 0.04) decreased at month 6 (0.59 ± 0.39 log MAR) compared to the mean BCVA at month 3 (0.44±0.28 log MAR). At the month 6, the mean CFT (411 mm, range 174–776 mm) (p < 0.001) was still significantly lower compared to the baseline value (517 mm, range 324–872 mm) (p = 0.01), but significantly increased compared to the mean CFT at month 3 (314 mm, range 186–758 mm). [20]

In the study on DEX implant in patients with persistent diabetic macular edema, Cerman and coworkers presented that the highest mean BCVA gain (0.58±0.36 log MAR) and central foveal flattening (286.9±79.9 mm) was achieved at first month, but there were no significant difference (0.88±0.43 log MAR, 0.70±0.43 log MAR; 577.6±265.8 mm, 414.3±157.5mm) at the months 6 and 12 compared to baseline value (0.76±0.37 log MAR, 518.0±149 mm).[21]

Calllanan and coworkers suggested that mean average BCVA change from baseline over 12 months was 4.34 letters with DEX implant versus 7.60 letters with ranibizumab. Kaplan–Meier analysis of time to achievement of ≥15-letter BCVA improvement showed that patients in the DEX implant group usually achieved ≥ 15-letters BCVA gain within 4 months after first DEX implant treatment. At month 12, the mean change from baseline CRT was similar in the DEX implant and ranibizumab groups (−173.9 and −163.5 μm respectively).[22]

In our study, there were 21 eyes (56.7%) with baseline VA≤ 0.7 Log MAR in the RAN group and 26 eyes (92.8%) with baseline VA≤ 0.7 Log MAR in the DEX implant group. In 21 patients in the RAN group, BCVA improvement was one-order in 6 eyes, 2-order in 5 eyes, 3-order in one eye, and 4-order in one eye at the month 6 whereas 4-order in 3 eyes, 5-order in 6 eyes, 6-order in 2 eyes, 7-order in 2 eyes, 8-order in 3 eyes, 9-order in 2 eyes at the month 12. In 26 patients in DEX group, BCVA improvement was one-order in 9 eyes, 2-order in 3 eyes, 4-order in one eye, 5-order in one eye at the month 3 whereas 1-order in 3 eyes, 2-order in one eye, 3-order in one eye, 4-order in one eye, 5-order in one eye at the month 6 whereas one-order in 8 eyes, 2-order in 6 eyes and 3-order in 4 eyes at the month 12.

The GENEVA study showed that an intravitreal DEX implant was associated with a low ocular risk profile.[23] In the present study, glaucoma was detected in 8 patients in the DEX group and was under control with topical medication. Cataract progression was observed in 2 cases in DEX group during the follow-up. No adverse effect was observed including inflammation, infection, thromboembolic events, or ocular toxicity associated to intravitreal DEX implant.

The effectiveness of a PRN regimen in DMO has been established with ranibizumab 0.5 mg (Lucentis®; Genentech, South San Francisco, California, USA; and Novartis Pharma AG, Basel, Switzerland) in the long-term RESTORE and DRCR.net (protocol I) studies In these studies, the initial best-corrected visual acuity (BCVA) improvements observed at year 1 were maintained through years 2, 3 and 5 with a reduced number of injections.[24, 25]

This study was limited by a retrospective cohort design, small number of non-naïve patients, DEX injections at per six months, differences of baseline VA rates between groups.

Consequently, DEX implant therapy does not seem as effective as intravitreal RAN therapy. DEX implant group could not maintain BCVA and CFT as well as intravitreal RAN group due to deferred DEX implant treatment. DEX therapeutic regiments should be customized for patients needs prior to at month 5 as every 16 weeks. Further comparative clinical trials are required to define the effect of intravitreal DEX implant and intravitreal RAN injections in a larger series with longer follow-up.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or non-profit sectors. We owe special thanks to Assistant Professor Dr. Bulent Ozkan PhD, Department of Biostatistics for helping with statistically evaluation of the study.

Conflict of interest

Authors declare no conflict of interest

Financial Disclosure

The authors declared that this study received no financial support.

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