Early Switch to Dexamethasone Implantation In Patients With Diabetic Macular Edema Resistant To Aflibercept: Short-Term Results

Aflibercept'e Dirençli Diyabetik Maküla Ödemi Olan Hastalarda Deksametazon Implantına Erken Geçiş: Kısa Dönem Sonuçlar

Alper Halil BAYAT[1], Burak ERDEN[1], Akın ÇAKIR[1], Selim BÖLÜKBAŞI[1], Emine BAŞ[2], Mustafa Nuri ELÇİOĞLU[3]

ABSTRACT

Purpose: To evaluate the efficacy of early switch to intravitreal dexamethasone implantation (IDI) in aflibercept resistant diabetic macular edema (DME)

Materials and methods: In this retrospective study 21 eyes of 21 patients with persistent diabetic macular edema, who underwent a single dose IDI were examined. All of the patients had a history of at least five intravitreal aflibercept (IVA) injections. Main outcome measures were changes in best-corrected visual acuity (BCVA), central macular thickness (CMT) at 1, 2, 3 months after IDI treatment.

Results: Mean follow-up time and average number of previous IVA injections was 19.24±1.67 months and 5.35±0.6. The mean BCVA was improved from 0.73±0.57logMAR to 0.49±0.34logMAR (p=0.011), 0.34±0.29 logMAR(p=0.001), and 0.36±0.27 logMAR(p=0.001) at 1,2 and 3 months, respectively. The mean CMT was decreased from 434±90 µm to 335±74 µm (p<0.001), 328±46 µm (p<0.001) and 350±85 µm (p=0.009) at 1,2 and 3 months.

Conclusion: Intravitreal dexamethasone implantation resulted in a significant improvement in visual and anatomical outcomes in patients with aflibercept resistant diabetic macular edema.

Key words: Dexamethasone, Diabetic macular edema, Optical coherence tomography.

ÖZ

Amaç: Aflibercepte dirençli diyabetik maküla ödeminde (DMÖ) deksametazon implantına (Dİ) erken geçiş yapılmasının etkinliğini araştırmak

Gereç ve yöntemler: Aflibercepte dirençli DMÖ ile tek doz Dİ uygulanan 21 hastanın gözü geriye dönük olarak incelendi. Hastaların hepsi en az 5 aflibercept enjeksiyonu almışlardı. Ana sonuç ölçütleri olarak DI tedavisinden sonraki 1. 2. ve 3. aylardaki en iyi düzeltilmiş görme keskinliği (EİDGK) ve santral maküler kalınlıklardaki (SMK) değişimler alınmıştır.

Bulgular: Ortalama takip süresi 19.24±1.67 ay ve ortalama aflibercept enjeksiyon sayısı 5.35±0.6'idi. EİDGK 0.73±0.57 logMAR'dan 1. ayda 0.49±0.34logMAR'a (p=0.011), 2. ayda 0.34±0.29 logMAR'a (p=0.001) ve 3. Ayda 0.36±0.27 logMAR'a (p=0.001) yükselmiştir. Ortalama SMK değeri 1. ayda 434±90 µm'den 335±74 µm'ye (p<0.001), 2. Ayda 328±46 µm'ye (p<0.001) ve 3. ayda 350±85 µm'ye (p=0.009) düşmüştür.

Sonuç: Deksametazon implantı aflibercepte dirençli DMÖ hastalarında istatiksel olarak anlamlı bir görme ve anatomik kazanım sağlamıştır.

Anahtar kelimeler: Deksametazon, diyabetik maküler ödem, optik kohorens tomografi

1- Uz. Dr., Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

2- Asist. Dr.. Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

3- Prof. Dr.. Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

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Yazışma Adresi / Correspondence Adress:
Alper Halil BAYAT
Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

Phone: +90 505 218 1959
E-mail: alperhalil76@hotmail.com

INTRODUCTION

Diabetic macular edema (DME) is the leading cause for visual acuity lost in diabetic patients.[1]DME may occur as a result of diffuse leakage of retinal vascular structure in macular or focal leakage of micro aneurysms. The pathogenesis of DME are an increase in inflammatory cytokines such as interleukin-6 and interleukin-8, vascular endothelial growth factor (VEGF) and prostaglandins in ocular fluids [2,3].Current practice indicates that intravitreal anti-VEGF therapies have been proven to be efficacious in terms of central macular thickness reduction and visual gain.[4-6] Nevertheless, not all of the patients respond to anti-VEGF treatment. Corticosteroids which are blocking VEGF, inflammatory cytokines and prostaglandins have anti-inflammatory, anti-angiogenic and anti-permeability effects.[7,8] Due to these effects, corticosteroids can be good options for treatment of DME.

Triamcinolone had been used in treatment of DME. Although intravitreal triamcinolone had been shown to result in improved anatomical and functional outcomes, its usage decreased because of safety concerns.[9,10]

Dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) is a sustained-release drug delivery system approved by FDA for treatment of DME.[11,12] Dexamethasone implant has six time stronger effects than intravitreal triamcinolone acetonide.[12]

The purpose of the current study is to evaluate the efficacy of early switch to dexamethasone implant (IDI) in patients with diabetic macular edema resistant to aflibercept.

METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki. All necessary authorizations were obtained from the Institutional Review Board of Okmeydanı Research &Traning Hospital, İstanbul, Turkey.

In this retrospective study we evaluated 21eyes of 21 patients which underwent a single dose IDI because of persistent DME that were unresponsive to aflibercept at Okmeydanı Research&Traning Hospital between January of 2016 and January of 2018. All of the patients had a history of at least five IVA injections. The last IVA injection was performed 1 month before IDI. Persistent DME was defined as macular edema of which CMT>300 µm with reduction in CMT less than 50 µm or increase in CMT measured with spectral domain optical coherence tomography (SD-OCT) after at least five continuously IVA injections. The pseudophakic patients were chosen to exclude cataract progression effect of dexamethasone.

Patients with a history of glaucoma, steroid induced ocular hypertension, vitroretinal surgery, other vitreoretinal diseases and retinopathies, IVA injections and laser photocoagulation within 3 months follow-up time were excluded.

Firstly, we evaluated CMT, BCVA, number of anti-VEGF injections before IDI and after three months follow-up period and HbA1c levels. Second, CMT and BCVA were evaluated before IDI and 1.2. 3. month after IDI. After IDI follow up period, necessity of anti-glaucomatous treatment, final CMT and BCVA were recorded.

All of the patients had standard ophthalmic examinations before treatment and post-treatment (1. 2. 3. months). The examinations included slit-lamb microscopy, BCVA, tonometer, SD-OCT, indirect ophthalmoscopy. The BCVA was measured with snellen chart, and the decimal visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR) units for the statistical analyses. Fundus fluorescein angiography (FFA) was performed at baseline. The patients which have macular ischemia in FFA were excluded. The patients with peripheral ischemia or neovascularition were treated with panretinal photocoagulation prior to anti-VEGF treatment.

The OCT acquisition was performed on the SD-OCT(Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg,Germany) the integrated follow-up mode of the device was used to ensure that the exact same retinal area was imaged at every follow-up visit.

Statistical analyses were performed using the SPSS software version 21. Descriptive analyses were presented using means and standard deviations for normally distributed variables. An assessment of normality was done using Kolmogorov-Smirnov test. The change in CMT and BCVA by time was investigated using repeated measures analysis of variance (repeated measures of ANOVA) and 2-related samples test. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

A total of 21 eyes were included in this study. 9 of the 21 patients were female (42%). All patients had type II diabetes mellitus. The patients who received a single dose IDI for treatment of aflibercept resistant DME were analyzed. The baseline characteristics of the patients are presented in table-1.

Table 1. *Baseline characteristics and demographics of the patients.*	
Patients	21
Age	58.8±11.4 years
Female/Male	9/21
Pseudophakia	21(100%)
Mean HbA1C	7.56±0.97
Duration of diabetes	19.2±1.6 years
Baseline BCVA	0.70±0.41 logMAR
BCVA after IVA treatment	0.73±0.57 logMAR
Baseline CMT	403±96 µm
CMT after IVA treatment	434±90 µm
Mean number of IVA injections	5.35±0.6
Panretinal LFK	6/21 (28%)
NDR/PDR	17/4
BCVA: best-corrected visual acuity; **CMT:** central macular thickness; **IVA:** intravitreal aflibercept **LFK:** laser photocoagulation, **NDR:** non-proliferative diabetic retinopathy, **PDR:** proliferative diabetic retinopathy	

Changes in visual acuity

Baseline BCVA was0.70±0.41 logMAR, after IVA treatment this number was 0.73±0.57 logMAR. After IDIthe mean BCVA was improved to 0.49±0.34 (p=0.011), 0.34±0.29 (p=0.001), and 0.36±0.27 (p=0.001)at 1,2 and 3 months, respectively. This improvement trend was statistically significant (p<0.001). The change in BCVA over time was illustrated in Figure 1.

Changes in macular thickness

The baseline CMT was 403±96 µm, after IVA treatment the mean CMT was found to be 434±90 µm. Compared to after IVA treatment CMT values, the mean CMT was decreased to 335±74 µm (p<0.001), 328±46 µm (p<0.001) and 350±85 µm (p=0.009) at 1,2 and 3 months, respectively. The mean CMT was increased at 2 month compared to 3 month, but this increase was not statistically significant (p>0.05). The change in CMT is presented in figure 2.

Safety outcomes

Only one patient had increase in IOP (IOP>21) (4.76%). The IOP was controlled with an anti-glaucomatous.

DISCUSSION

Anti-VEGF and steroids are nonsurgical treatment options for DME. Sometimes, DME do not respond well to anti-VEGF injections. This may be because of pro inflammatory cytokines other than VEGF. Therefore, it may be efficacious to switch from anti-VEGF to steroids because of corticosteroids' anti-inflammatory effects.

Previous studies had shown thatdexamethasone implantation was successful in terms of anatomical and visual gain in patients with macular edema persistent to ranibizumab and

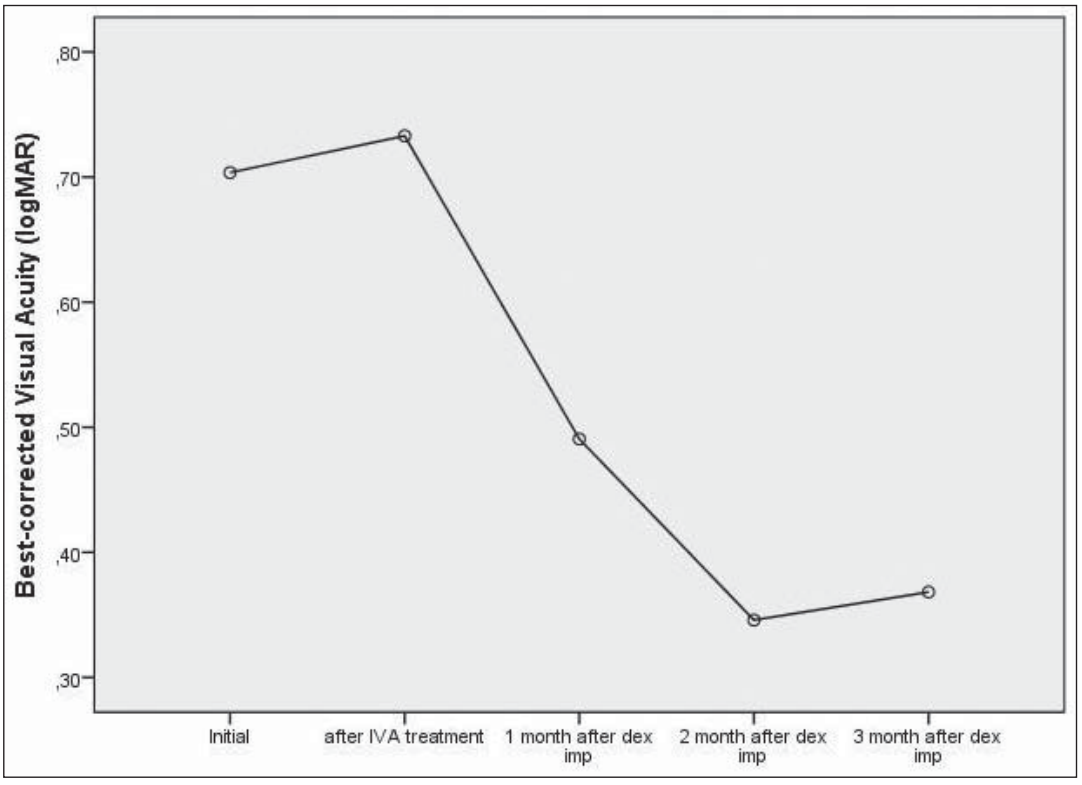


Figure 1. *Changes in best corrected visual acuity (BCVA) after dexamethasone implantation.*

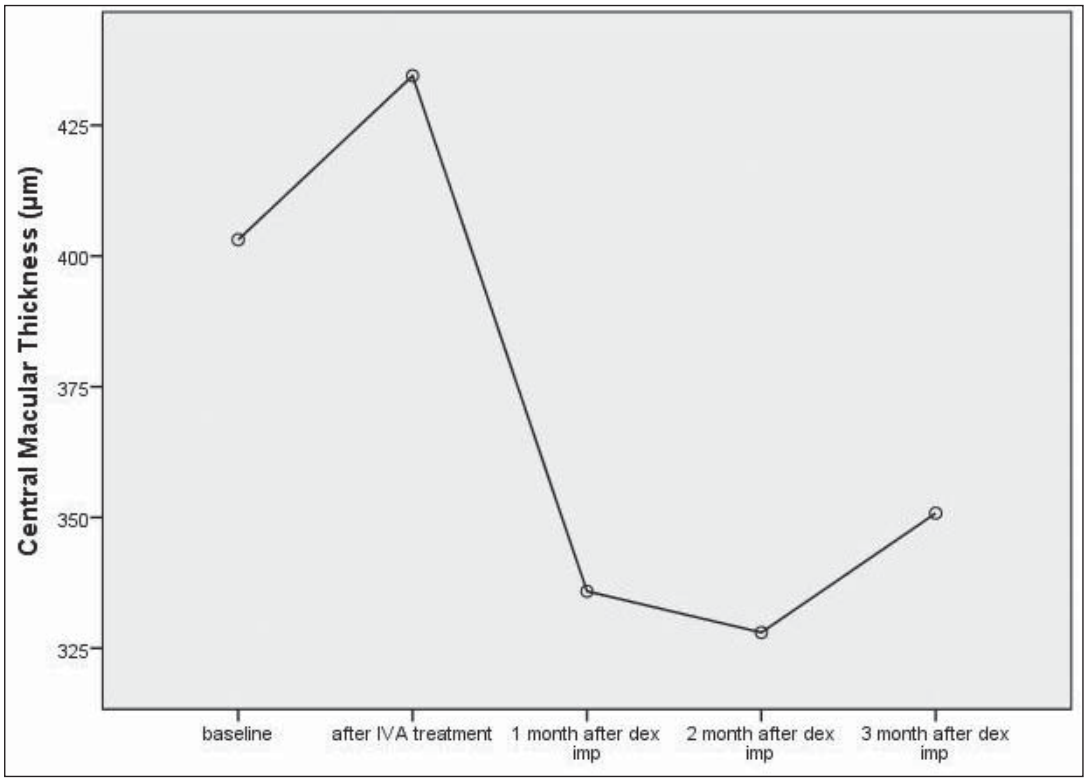


Figure 2. *Changes in central macular thickness (CMT) after dexamethasone implantation.*

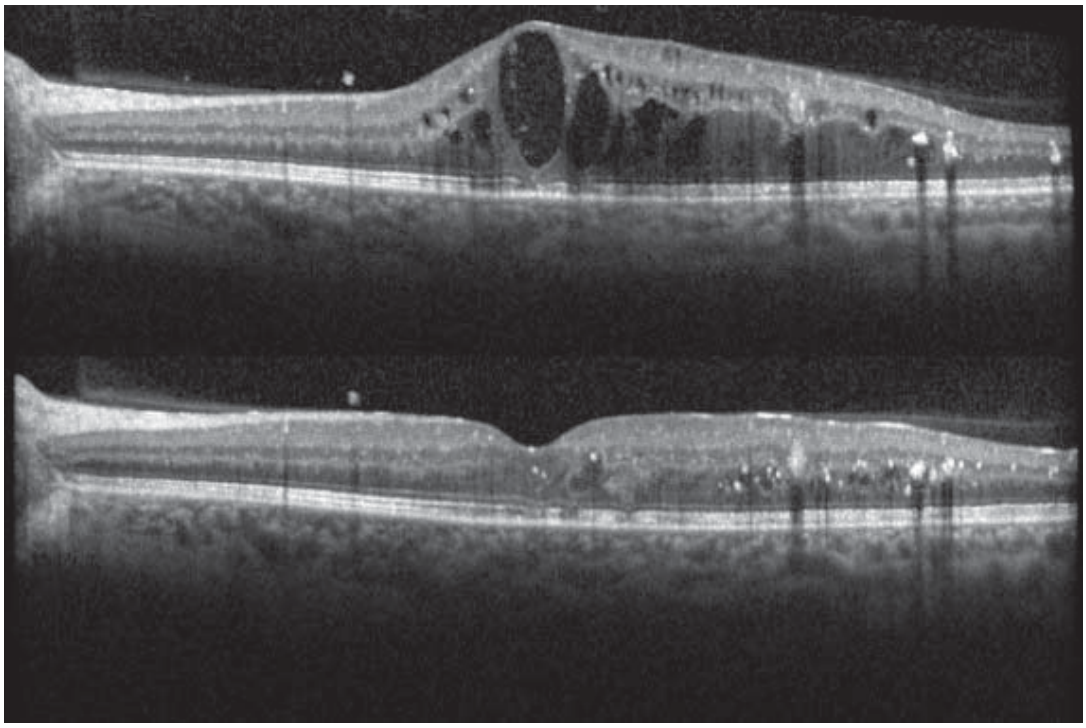
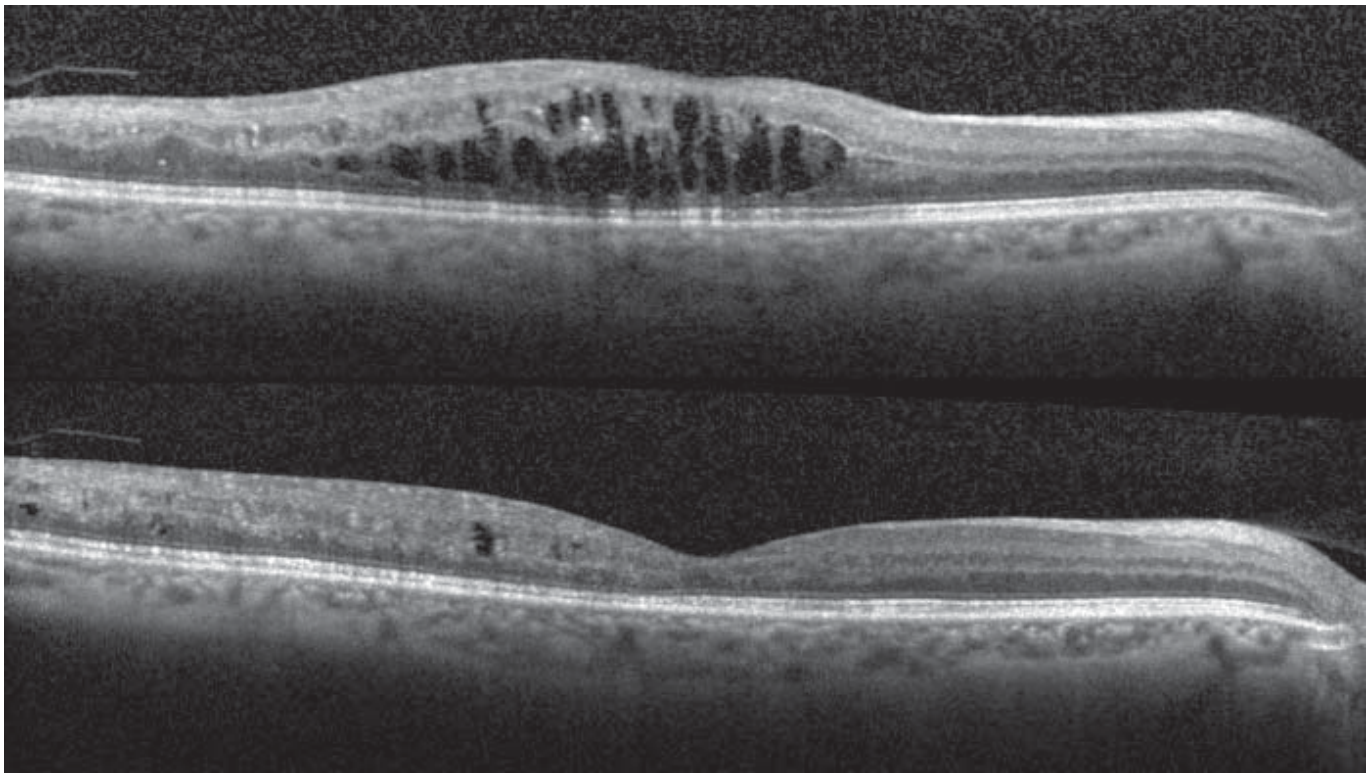


Figure 3. *Optical coherence tomography images of some patients before and after the dexamethasone treatment.*

bevacizumab.[13-21] In the study they performed, Totan et al. showed that the IDI provides visual and anatomical gain during the first three months in patients who have received IDI after at least an average number of 6 bevacizumab injections.[21]. Zohioua et al showed that IDI are effective in patients who has received 6 continuously 6 ranibizumab injections.[22] The common feature of both studies is that they do not continue with anti-VEGFs and switch to IDI after 6 intravitreal injections.The early switch to IDI was found to be useful in these studies.



5 loading dose of aflibercept have been recommended in VIVID and VISTA studies.[23] In another study bevacizumab, ranibizumab and aflibercept were compared in DME. In that studyaflibercept was found to be superior in terms of both visual and anatomical gain in DME at the end of the first year.[24] Although in the second year this superiority was only to bevacizumab, the results of the first year is important to explain switch in our study. In posthoc analysis of DRCR.net, aflibercept was found to be more effective especially for eyes with initial BCVA 20/50 or worse.[25] In a recent study, Neil M. Bressler and et al. show that 31.6% of the patients treated with aflibercept had persistent DME. The cumulative probability that these eyes manifested persistent DME with aflibercept was 44.2% at 2 years.[26] In that study, almost half the patients who were resistant at the end of the sixth month were found to be resistant at the end of the second year.This means that if the patients with resistant DME(with low visual acuity) continue to be treated with aflibercept, the life quality of almost half patients will be adversely affected for 1.5 years. It is important to note that aflibercept has a rapid effect on recovery, 5 loading dose are recommended, in the first year aflibercept is more effective than other anti-VEGFs and half the patients who are resistant to aflibercept at sixth month will be still resistant to DME. With all of these thought in mind, we did not continue with aflibercept and performed IDI after at least 5 IVA injections to our patients

In the current study results have revealed that patients had significantly anatomical and functional outcomes over 3 months after IDIfor DME persistent to aflibercept (at least five monthly IVA injections). 1 month after IDICMT decreased significantly, but after 3 month an increase can be seen in CMT. This is similar to other switch studies, IDI effects can be maintained 3 or 4 months.[13-21] Similar to anatomical gain, there was a significantly visual gain after dexamethasone implantation. It can be considered that this effect is due to the anti-inflammatory effect of the steroids. Even when the levels of VEGF are suppressed by aflibercept, sometimes they may not show sufficient anti-inflammatory activity. It may be necessary to perform switch with the steroids. But when to make switch is the main thing to be considered. In a recent study,it has been discussed whether the switch should be performed early in patients with suboptimal response to anti-VEGFs.[27] In that study, suboptimal response was defined as ≤5 letter gain in BCVA (including vision loss) or reduction of less than 20% of CMT on SD-OCT one month after third injections. The patients were divided into two groups: some patients were received IDI after three monthly anti-VEGF injections, the other patients were treated with continuously anti-VEGFs. The patients which switched to IDI has higher visual and anatomical gain than the patients with treated anti-VEGFs at the end of the first year. In that study, IDI switch was performed after three monthly aflibercept injections.Unlike that study, we performed five loading dose of aflibercept as recommended and then switched on. Both studies explain that the patients who have insufficient response to aflibercept can benefit from early switch to IDI. If we think that we are

aiming to increase the quality of life of the patients, early switch to IDI should not be overlooked in patients who have insufficient response to aflibercept.

Our study has some limitations. First, our study has small number of patients. Second, this was a retrospective design. Third, we have only three months data, but we want to explain short term results of our study.

CONCLUSION

Early switch of intravitreal dexamethasone implantation resulted in a significant improvement in visual and anatomical outcomes in eyes with refractory DME despite previous treatment with IVA. If we consider the side effects of dexamethasone implantation such as cataract development and IOP increase, we recommend dexamethasone implantation in non-glaucomatous patients with pseudophakic eyes.

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