

# 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 Dekametazon Implantına Erken Geçiş: Kısa Dönem Sonuçlar

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### 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, we reviewed 21 eyes of 21 patients with persistent diabetic macular edema who underwent a single dose IDI. All patients had a history of treatment with at least five intravitreal aflibercept (IVA) injections. Main outcome measures were changes in best-corrected visual acuity (BCVA), central macular thickness (CMT) at months 1, 2, 3 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 months 1,2 and 3, 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 months 1, 2 and 3.

**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 Dİ 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:** Dekametazon implantı aflibercepte dirençli DMÖ hastalarında istatistiksel olarak anlamlı bir görme ve anatomik kazanım sağlamıştır.

**Anahtar kelimeler:** Dekametazon, diyabetik maküler ödem, optik kohorens tomografi

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## INTRODUCTION

Diabetic macular edema (DME) is the leading cause for loss of visual acuity in diabetic patients.<sup>1</sup>DME may occur as a result of diffuse leakage of retinal vascular structure in macula or focal leakage of micro aneurysms. The DME pathogenesis includes 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 regarding central macular thickness reduction and visual gain.<sup>4-6</sup> Nevertheless, not all of the patients respond to anti-VEGF treatment. Corticosteroids, which block VEGF, inflammatory cytokines and prostaglandins, have anti-inflammatory, anti-angiogenic and anti-permeability effects.<sup>7,8</sup> Due to these effects, corticosteroids can be good option for DME treatment.

Triamcinolone have been used in DME treatment . Although intravitreal triamcinolone was shown to improve anatomical and functional outcomes, its usage decreased because of safety concerns.<sup>9,10</sup>

Dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) is a sustained-release drug delivery system approved by FDA for DME treatment.<sup>11,12</sup> Dexamethasone implant has 6-folds stronger effects than intravitreal triamcinolone acetonide.<sup>12</sup>

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 & Training Hospital, İstanbul, Turkey.

In this retrospective study, we evaluated 21 eyes of 21 patients which underwent a single dose IDI because of persistent DME that were unresponsive to aflibercept at Okmeydanı Research & Training Hospital between January of 2016 and January of 2018. All patients had a history of treatment with 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 <50 µm reduction in CMT 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 effect of dexamethasone on cataract progression.

Patients with a history of glaucoma, steroid-induced ocular hypertension, vitreoretinal 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 3 months of follow-up and HbA1c levels. Secondly, CMT and BCVA were evaluated before IDI and at months 1, 2, and 3 after IDI. After IDI follow-up period, need for anti-glaucomatous treatment, final CMT and BCVA were recorded.

All patients had standard ophthalmic examinations before and after treatment (at months 1, 2 and 3). The ophthalmologic examination included slit-lamb microscopy, BCVA, tonometry, SD-OCT and indirect ophthalmoscopy. The BCVA was measured with Snellen charts 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 who had macular ischemia in FFA were excluded. The patients with peripheral ischemia or neovascularization were treated with panretinal photocoagulation prior to anti-VEGF treatment.

The OCT scanning was performed using SD- OCT (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany). The integrated follow-up mode 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 are presented as mean and standard deviation in variables with normal distribution. The normal distribution was assessed using Kolmogorov-Smirnov test. The change in CMT and BCVA over time was analyzed using repeated measures analysis of variance (repeated measures of ANOVA) and paired-sample t test. A p value<0.05 was considered as statistically significant.

## RESULTS

Overall, 21 eyes were included in this study. Of 21 patients, 9 (42%) were female. 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.

<b>Table 1:</b> 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
<b>BCVA:</b> best-corrected visual acuity; <b>CMT:</b> central macular thickness; <b>IVA:</b> intravitreal aflibercept <b>LFK:</b> laser photocoagulation, <b>NDR:</b> non-proliferative diabetic retinopathy, <b>PDR:</b> proliferative diabetic retinopathy	

#### Changes in visual acuity

The mean BCVA was 0.70±0.41 logMAR at baseline and 0.73±0.57 logMAR after IVA treatment. After IDI, the 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 months 1, 2 and 3, respectively. The improvement trend was statistically

significant ( $p<0.001$ ). The change in BCVA over time was illustrated in Figure 1.

#### Changes in macular thickness

The mean CMT was 403±96 μm at baseline and 434±90 μm after IVA treatment. When compared post-IVA 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 months 1, 2 and 3, respectively. The mean CMT was increased at month 2 compared to month 3, but the increase was not statistically significant ( $p>0.05$ ). The change in CMT is presented in figure 2.

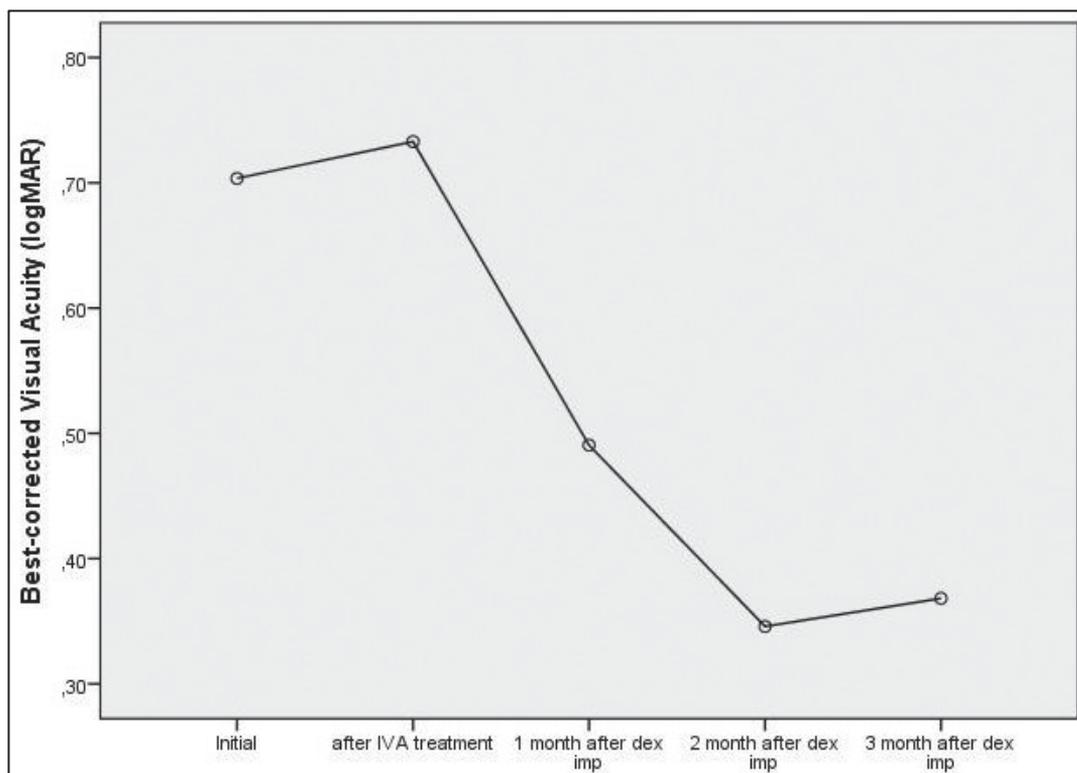
#### Safety outcomes

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

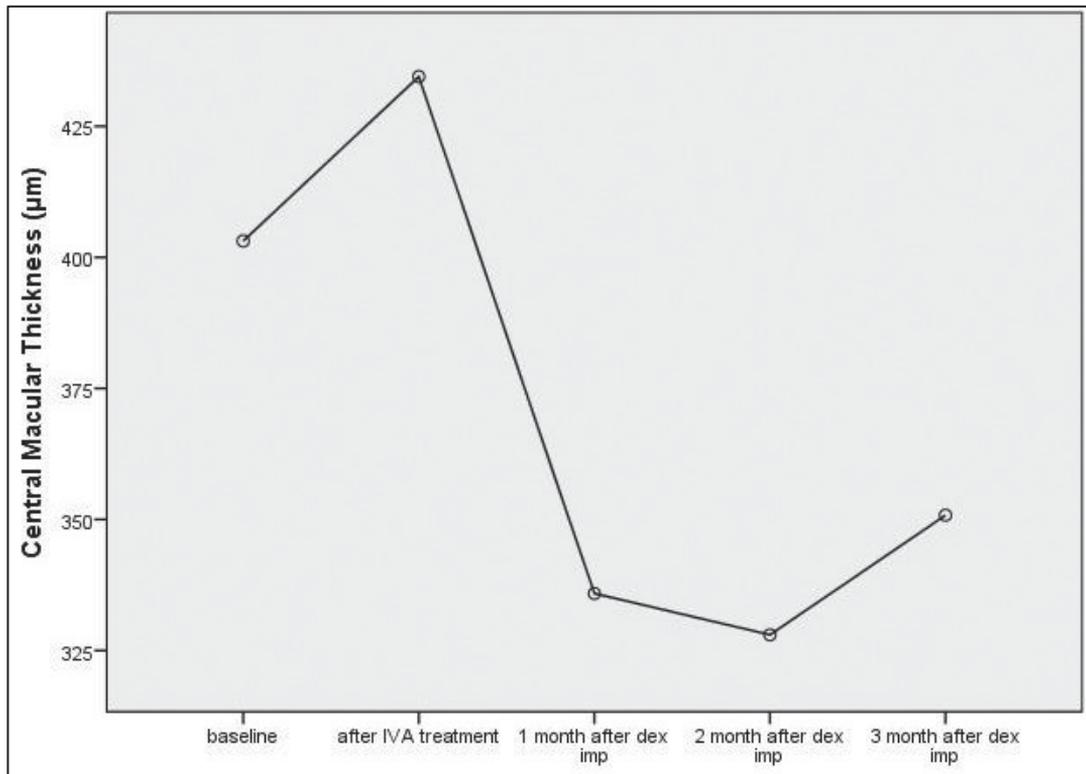
#### DISCUSSION

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

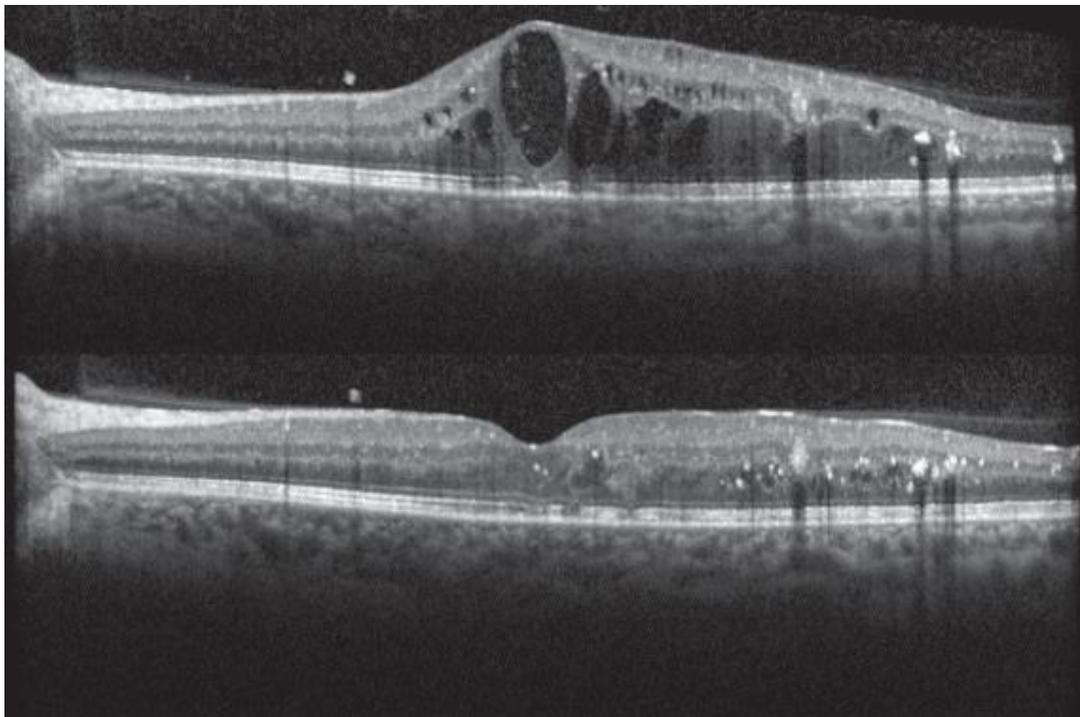
Previous studies showed that dexamethasone implantation was successful regarding anatomical and visual gain in patients with macular edema persistent to ranibizumab and



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



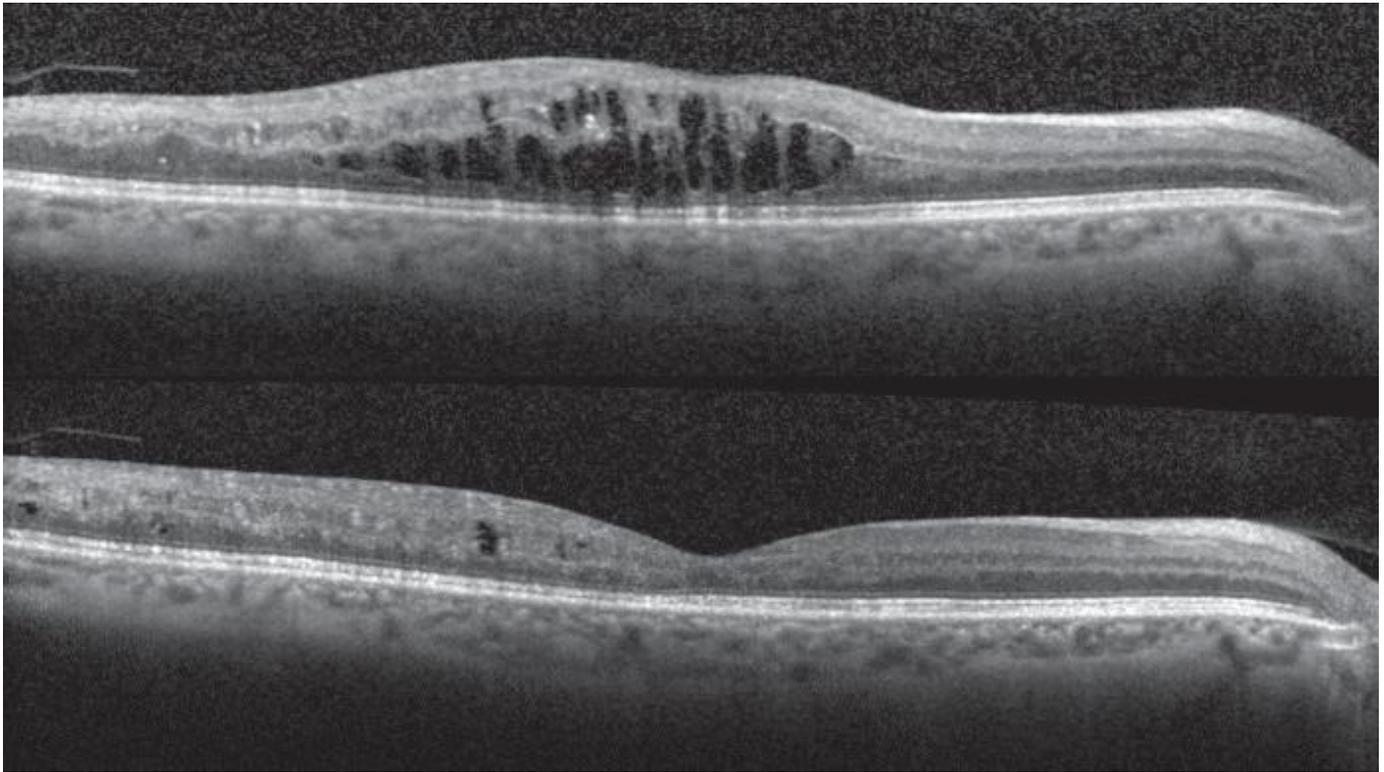
**Figure 2:** Changes in central macular thickness (CMT) after dexamethasone implantation.



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

bevacizumab.<sup>13-21</sup> In a study by Totan et al., it was shown 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.<sup>21</sup> Zohioua et al. showed that IDI are effective in

patients who has received 6 continuously ranibizumab injections.<sup>22</sup> 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.



In VIVID and VISTA studies, 5loading dose of aflibercept have been recommended.<sup>23</sup> In another study, bevacizumab, ranibizumab and aflibercept were compared in DME. In that study, aflibercept was found to be superior regarding both visual and anatomical gain in DME at the end of the first year.<sup>24</sup> Although, in the second year, the superiority was only valid for bevacizumab, the results of the first year is important to explain switch in our study. In the post-hoc analysis of DRCR. net, aflibercept was found to be more effective especially in eyes with initial BCVA 20/50 or worse.<sup>25</sup> In a recent study, Neil M. Bressler and et al. showed that 31.6% of the patients treated with aflibercept had persistent DME. The cumulative probability for persistent DME with aflibercept was 44.2% at 2 years.<sup>26</sup> 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. Given these, we did not continue with aflibercept and performed IDI after at least 5 IVA injections in our patients

In the current study, results revealed that patients had significantly better anatomical and functional outcomes over

3 months after IDI for DME persistent to aflibercept (at least five monthly IVA injections). One month after IDI, CMT decreased significantly, but an increase can be seen in CMT after 3 months. This is similar to other switch studies and IDI effects can be maintained 3 or 4 months.<sup>13-21</sup> Similar to anatomical gain, there was a significantly better 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. However, 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.<sup>27</sup> In that study, suboptimal response was defined as  $\leq 5$  letter gain in BCVA (including vision loss) or  $< 20\%$  reduction in CMT on SD-OCT one month after third injection. The patients were divided into two groups: some patients were received IDI after three monthly anti-VEGF injections while other patients were treated with continuous anti-VEGFs. The patients which switched to IDI had 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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