# Ranibizumab Tedavisine Dirençli Diyabetik Makula Ödeminde Aflibercept Etkinliğinin Değerlendirilmesi

## Analysis of Response to Aflibercept in Diabetic Macular Edema Refractory to Previous Ranibizumab Theraphy

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### ÖZ

**Amaç:** İntravitreal ranibizumab (İVR) tedavisine dirençli diyabetik maküler ödemli (DMÖ) hastalarda intravitreal aflibersept (IVA) tedavisinin etkinliğinin değerlendirilmesi

**Gereç ve Yöntemler:** İVR tedavisine dirençli olup İVA tedavisine geçilen, DMÖ' lü toplam 21 hastanın 21 gözüne ait veriler retrospektif olarak incelendi. Hastaların tedavi öncesi, IVR tedavisi sonrası ve IVA tedavisine geçildikten 6.aydaki anatomik ve görsel verileri karşılaştırıldı. DMÖ tipinin sonuçlar üzerine olan etkisi ve prediktif faktörler çoklu doğrusal regresyon modeli kullanılarak ayrıca çalışıldı.

**Bulgular:** Olgulara IVA tedavisine geçilmeden önce uygulanmış olan ortalama IVR enjeksiyon sayısı 6,1±1,4 (5-9) idi. Ortalama IVA enjeksiyon sayısı 3,3±0,5 (3-5) idi. Olguların ortalama santral makula kalınlık (SMK) değeri başvuru anında 426,3±91,7 µm, IVR tedavisi sonrası 417,6±80,8 µm; IVA tedavisi sonrası 6.ayda 285,7±46,8 µm olarak bulunmuştur (p<0,001). Olguların ortalama en iyi düzeltilmiş görme keskinliği (EDGK) değerleri başvuru anında 0,5±0,3 Logmar; IVR tedavisi sonrası 0,3±0,2 Logmar; IVA tedavisi sonrası 6.ayda 0,16±0,15 Logmar olarak saptanmıştır (p<0,001). Diffüz retinal kalınlaşma olgularının IVA tedavisine anatomik açıdan diğer DMÖ tiplerine göre daha iyi yanıt verdikleri gözlemlenmiş iken (p=0,044), EDGK bu olgularda sınırlı yükselme göstermiştir. SMK üzerine IVA enjeksiyon sayısı (B= -53,8, p=0,002), EDGK üzerine ise DMÖ tipi (B=0,206, p<0,001) en etkili faktör olarak saptanmıştır.

**Sonuç:** IVR tedavisine dirençli DMÖ hastalarında IVA tedavisine geçiş anatomik ve görsel iyileşme sağlamaktadır.


**Anahtar Kelimeler:** İntravitreal ranibizumab, intravitreal aflibersept, diyabetik maküler ödem.


### ABSTRACT

**Objectives:** To determine the efficacy of intravitreal aflibercept (IVA) in the patients with diabetic macular edema (DME) refractory to previous intravitreal ranibizumab (IVR) treatment.

**Materials and Methods:** A total of 21 eyes of 21 patients who were switched to IVA therapy due to recalcitrant DME to prior IVR treatment were studied retrospectively. The visual and anatomical parameters at baseline, after IVR treatment and on month 6 after initial IVA injection were compared. The effect of DME type on the outcomes and the predictive factors were also evaluated by using a multiple linear regression model.

**Results:** The mean number of IVR injections was 6.1±1.4 (5-9) before switching. The mean number of IVA injections after switching was 3.3±0.5 (3-5). The mean central macular thickness (CMT) was 426.3±91.7 µm at baseline and 417.6±80.8 µm after IVR injections. After switching to IVA the mean CMT was decreased to 285.7±46.8 µm (p<0.001). The best corrected visual acuity (BCVA) was 0.5±0.3 Logmar at baseline and 0.3±0.2 Logmar after IVR injections. After switching to IVA, the mean BCVA was improved to 0.16±0.15 Logmar (p<0.001). The patients with diffuse retinal thickening responded better to IVA injections than the patients with other DME subtypes regarding to CMT (p=0.044). However, BCVA improvement was limited in those patients. The number of IVA injections was a good predictor for final CMT and the DME subtype was a good predictor for BCVA.

**Conclusion:** In patients with refractory DME to prior IVR injections, switching to IVA resulted in anatomical and visual improvement.


**Key Words:** Intravitreal ranibizumab, intravitreal aflibercept, diabetic macular edema.

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## INTRODUCTION

Diabetic macular edema (DME) is the most common causes of decreased visual acuity in patients with diabetic retinopathy and results from disruption of inner blood-retina barrier.[1] Today, the incidence of diabetes mellitus (DM) is rapidly increasing; thus, DME frequency is also increased in parallel to DM incidence. In Turkey, there are approximately 6.680.107 people (aged>20 years) with DM.[2] Based on this figure, calculations relying on several prevalence studies estimate that there are 66.801-380.766 people suffer from DME.[3,4,5]

In DME, current treatment modalities include laser photocoagulation (LFC), intravitreal anti-vascular endothelial growth factor (-VGEF) therapy, intravitreal steroid and vitrectomy.[6] Given studies evidenced that intravitreal anti-VGEF is superior against LFC and long-term adverse effect profile of intravitreal steroid therapy, intravitreal anti-VGEF therapy is preferred as first-line treatment in our clinic practice.[7,8] Intravitreal bevacizumab (IVB) is used as off-label agent while intravitreal ranibizumab (IVR) and intravitreal aflibercept (IVA) were approved by FDA. It was shown that above-mentioned anti-VGEF agents are equally effective in the treatment of DME.[9]

The fact that desired improvement could not be achieved in some cases promoted that switching to another anti-VGEF agent may be possible in refractory DME cases. In this study, our aim was to assess anatomic and visual outcomes in IVA therapy and predictive factors in DME cases refractory to previous IVR therapy.

## MATERIAL AND METHOD

The study included 21 eyes of 21 patients with DME who were managed in Retina Department of Okmeydanı Training and Research Hospital and were switched to IVA treatment due to refractoriness to previous IVR treatment. The study was approved by Ethics Committee on Clinical Studies of Health Sciences University, Okmeydanı Training and Research Hospital. The study was conducted in accordance to Declaration of Helsinki.

We retrospectively reviewed files of patients included. Data regarding time of presentation, best corrected visual acuity (BCVA) after IVR treatment and on month 6 after switching IVA treatment, total number of IVR and IVA injections, central macular thickness (CMT), intraocular pressure (IOP), HbA1c values, presence of serous macular detachment-cystoid changes and/or diffuse edema, DRP stage, cataract and/or glaucoma development during follow-up, insulin use and argon laser photocoagulation administration were recorded. It was taken care to find written informed consent before injection in all files.

The patients with history of pars plana vitrectomy and grid laser photocoagulation, those with vitreomacular interface pathology that may affect treatment outcome and those with poor OCT quality were excluded.

The patients having CMT value>320 µm despite 5 consecutive monthly IVR injections, those having intra-retinal and/or sub-retinal fluid on OCT and patient failed to achieve ≥5 letters visual acuity gain were considered to have DME refractory to IVR treatment.

After switching IVA treatment, 3 loading doses (monthly) were administered; then, injections were repeated with PRN regimen if needed. The OCT studies were performed in all control visits and the results at the end of month 6 were included to the analysis.

All injections were performed using 30 G injector in operating theatre as being 0.5 mL in volume. The doses of ranibizumab and aflibercept were 0.5 mg and 2 mg, respectively.

OCT images were captured by using Cirrus HD-OCT (Carl Zeiss Meditech, Dublin, California, USA). Based on OCT image, DME was classified as cystoid macular edema (CME), serous macular detachment (SMD) and diffuse retinal thickening (DRT). The BCVA values were converted to "the logarithm of the minimal angle of resolution (logMAR)" unit for statistical purposes.

Statistical analyses were performed by SPSS version 15.0. The variance analysis of repeated measurements or Friedman test was used to assess changes over time when appropriate. The predictive factors for CMT decrease and BCVA gain were assessed by multivariate linear regression analysis. A p value<0.05 was considered as statistically significant.

## FINDINGS

We retrospectively reviewed data obtained over 6 months prior to IVA treatment in 21 eyes from 21 patients. Mean age was 59.1±6.5 years. Fifteen patients (71.4%) were male. Mean number of IVR injections before switching to IVA was 6.1±1.4. There was SMD in 7 patients (33.3%), CME in 12 patients (57.1%) and DRT in 2 patients (9.5%). During follow-up, cataract requiring surgery was developed in only 2 patients (9.5%) while no glaucoma development was observed. Table 1 presents demographic data of patients.

Mean CMT value was found to be 426.3±91.7 µm at baseline, 417.6±80.8 µm after IVR treatment and 285.7±46.8 µm on month 6 after IVA treatment. The decrease in CMT was found to be statistically significant (p<0.001) (Table 2).

Mean BCVA was found to be 0.5±0.3 Logmar at baseline, 0.3±0.2 Logmar after IVR treatment and 0.16±0.15 Logmar on month 6 after IVA treatment. The improvement in BCVA was found to be statistically significant (p<0.001) (Table 2).

| **Table 1:** *Demographic characteristics of patient (n=21) (IVR: Intravitreal ranibizumab, IVA: Intravitreal aflibercept, DME: Diabetic macular edema, SMD: Serous macular detachment, CME: Cystoid macular edema, DR: Diffuse retinal thickening)* | |
|---|---|
| Age (year) | 59.1±6.5 |
| Gender (male[%])<br>Mean HbA1c (mg/dl) | 15 [71.4%]<br>7.8±1.4 |
| Number of IVR injections | 6.1±1.4 |
| Number of IVA injections | 3.3±0.5 |
| DME type<br>SMD<br>CME<br>DRT | <br>7 [33.3%]<br>12 [57.1%]<br>2 [9.5%] |
| DRP tipi<br>Proliferative [%]<br>Non-proliferative [%]<br>Cataract formation [%]<br>Glaucoma[%]<br>Insülin use [%] | <br>2 [9.5%]<br>19 [90.5%]<br>2 [9.5%]<br>-<br>15 [71.4%] |

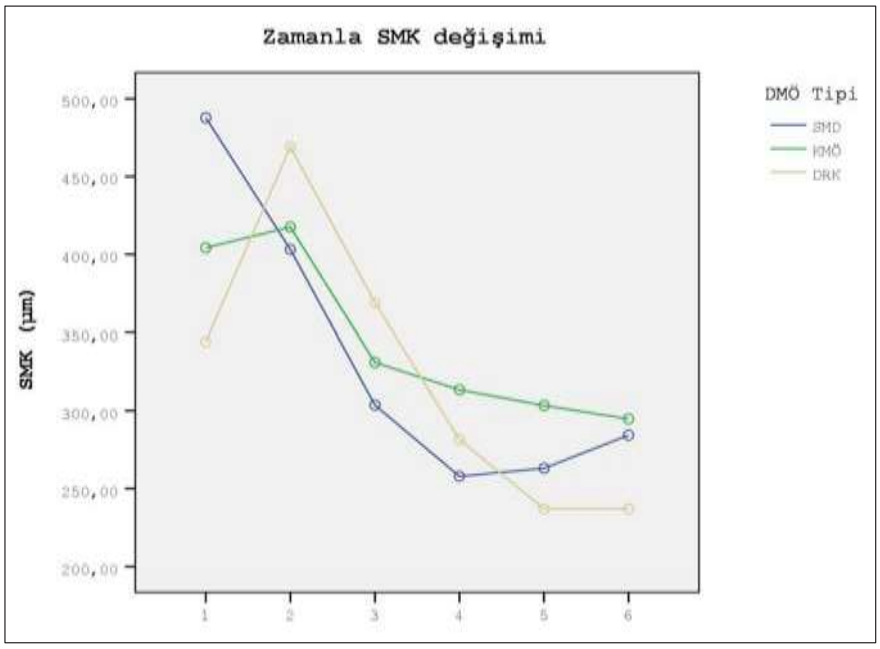
When treatment response was assessed according to DME type, it was observed that, compared to other DME types (SMD and CME), the cases with DRT was associated to better response to IVA treatment regarding anatomic outcome (decreased CMT) (p=0.044) (Picture 1). A similar trend was observed in visual acuity gain but did not reach statistical significance (p=0.079) (Picture 2).

When we assessed independent effects of several predictors (age, gender, HbA1c, number of injections etc.) on CMT by using a multivariate linear regression model, it was found that number of IVA injections and age were strongest predictors influencing on final CMT (B= -53.8,p=0.002; B= -4.4,p=0.004; respectively).

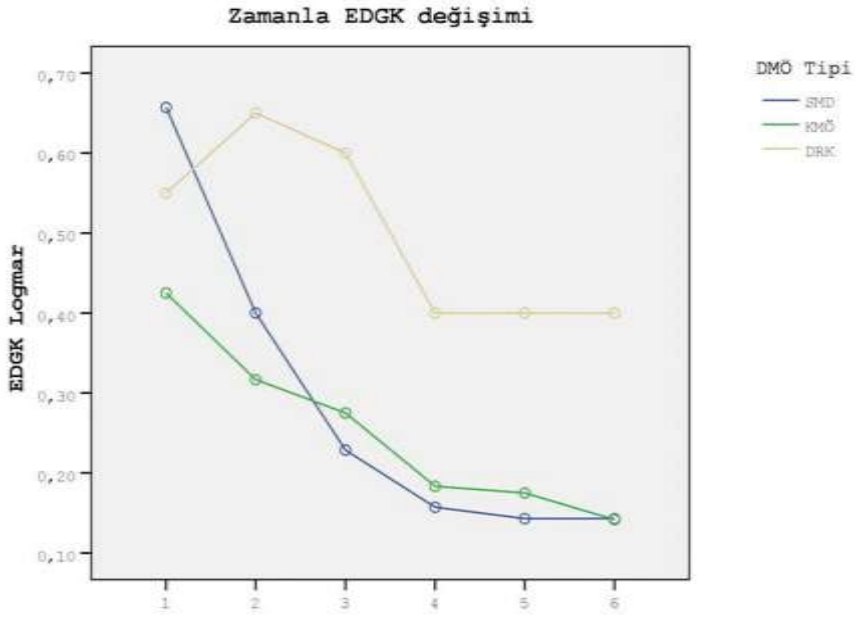
In the same analysis, it was found that DME type (B=0.206, p<0.001), HbA1c level (B= -0.036,p=0.041) and CMT value at presentation (B=0.001,p=0.001) were predictive for final BCVA.

**Table 2.** *The changes in CMT and BCVA over time (CMT: central macular thickness and BCVA: Best corrected visual acuity IVR: Intravitreal ranibizumab, IVA: Intravitreal aflibercept)*

| | Baseline | Post-IVR | IVA (month 1) | IVA (month 2) | IVA (month 3) | IVA (month 6) | P value |
|---|---|---|---|---|---|---|---|
| Mean CMT (µm) | 426.3±91.7 | 417.6±80.8 | 325.4±60.3 | 291.8±58.9 | 283.5±41.1 | 285.7±46.8 | <0.001 |
| Mean BCVA (Logmar) | 0.51±0.30 | 0.37±0.22 | 0.29±0.22 | 0.19±0.14 | 0.18±0.16 | 0.16±0.15 | <0.001 |




**Picture 1.** *Baseline, 2=After IVR treatment, 3=month 1 after IVA treatment, 4= month 2 after IVA treatment, 5= month 3 after IVA treatment, 6= month 6 after IVA treatment. CMT change over time according to DME type; it can be seen that BCVA was worsened after IVR therapy and responded to IVA treatment partially. (IVR: Intravitreal ranibizumab, IVA: Intravitreal aflibercept, DME: Diabetic macular edema, SMD: Serous macular detachment, CME: Cystoid macular edema, DRT: Diffuse retinal thickening, BCVA: Best corrected visual acuity)).*




**Picture 2.** *1= Baseline, 2=After IVR treatment, 3=month 1 after IVA treatment, 4= month 2 after IVA treatment, 5= month 3 after IVA treatment, 6= month 6 after IVA treatment. BCVA change over time according to DME type; it can be seen that BCVA was worsened after IVR therapy and responded to IVA treatment partially. (IVR: Intravitreal ranibizumab, IVA: Intravitreal aflibercept, DME: Diabetic macular edema, SMD: Serous macular detachment, CME: Cystoid macular edema, DRT: Diffuse retinal thickening, BCVA: Best corrected visual acuity)*

## DISCUSSION

In current literature, there are studies addressing switch to IVA treatment in DME cases refractory to IVR or IVB treatment. In majority of these studies, visual and anatomic success was reported after treatment.[10,11,12,13,14,15,16] Our results also favor previous findings. This effect may be due to different characteristics of aflibercept when compared to other 2 anti-VGEF agents. Aflibercept binds to VGEF-A in a more sustained manner with higher affinity when compared to bevacizumab and ranibizumab. In addition, unlike other two anti-VGEF agents, aflibercept also inhibits VGEF-B and platelet-derived growth factor (PDGR).[17] It has been reported that PDGF is increased together with VGEF in humor aqueous in DME and that it may play role in the DME pathogenesis.[18]

On the other hand, in a study by Rahimy et al., anatomic success was observed following IVA treatment but visual gain did not reach statistical significant11.[19] This may be due to time to switching IVA treatment and photoreceptor damage that might have been developed during this period. Authors reported mean number of IVR/IVB injections as 13.7 before IVA treatment. This figure was 6.1±1.4 in our study. In this perspective, we think that it is important to identify refractory DME in optimal time and to switch another anti-VGEF agent early by defining poor responders.

In our study, another striking finding was that the response to IVA treatment varies according to DME type. We observed that IVR was relatively inadequate in cases with DRT wit better response to IVA treatment. This may be due to longer half-life of aflibercept in vitreous (7.13 days in aflibercept vs. 4.75 days in ranibizumab) and better penetrance to retina in aflibercept. However, this finding should be interpreted cautiously due to smaller sample size in our study.

In our study, it was observed that number of IVA injections was most effective parameter on reduced CMT. However, we detected that other parameters (DME type, HbA1c, and baseline CMT) rather than number of IVA injections played key role in CMT reduction. The DRT cases were particularly interesting. The BCVA values improved at a certain level. This may be photoreceptor damage in DRT cases. We think that the decision to switch with another intravitreal agent should be made more quickly.

To best of our knowledge, there is no study addressing DME type and anti-VGEF response following switch or predictive factors in these patients.

In addition, all patients received IVB and/or IVR treatment before switch in all studies in the literature; however, only IVR treatment was used before IVA treatment in our study. This is first study in this perspective.

The major limitations are retrospective design and small sample size in this study. Not all patient received 5 loading dose as recommended in the protocol; thus, this may represent another limitation.

In conclusion, IVA seems as a safe and effective treatment alternative in DME cases refractory to IVR treatment.

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