RESEARCH ARTICLE

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Outcomes of Intra-Vitreal Ranibizumab Mono-Therapy and, Intra-Vitreal Ranibizumab and Intra-Vitreal Triamcinolon Combination Therapy in Diabetic Macular Edema

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Objective: To investigate the influences of intra-vitreal ranibizumab (IVR) monotherapy and IVR+intra-vitreal triamcinolon (IVTA) combination therapy on visual acuity (VA) and central foveal thickness (CFT) in treatment of diabetic macular edema (DME).

Materials and Methods: 52 eyes of 37 patients who had clinically significant DME were included in the study. All patients were initially administered 0.5 mg/0.05 ml ranibizumab via intra-vitreal route. Following 2 ranibizumab injections unresponsed cases were administered IVR+IVTA combination therapy. Visual acuity and CFT values compared before the injection, and at 1, 3 and 6th months after the injection.

Results: While mean visual acuity was 0.68±0.42 logMAR before the injection. A statistically significant increase was detected in visual acuity at the first and the third months as compared to pre-injection values (0.05). Although visual acuity increased also at the sixth month, the difference between groups was not statistically significant (p>0.05). Mean CFT value was 557.4±157.7 µm before the injection. A statistically significant decrease was detected at the controls of month 1, 3 and 6 as compared to pre-operative CFT (p<0.05). Mean VA was found to be 0,60±0,41 logMar and 0.58±0.38 logMar, respectively when the patients who were applied IVR and IVR+IVTA combination therapy were compared with regard to month 6 results; and mean CFT values were found to be 419.35±205.5 µm and 487.0±215.5 µm, respectively. No statistically significant difference was observed between two groups (p>0.05).

Conclusion: IVR+IVTA combination therapy may be an alternative method in resistant DME cases together with intra-vitreal ranibizumab monotherapy.

Key Words: *Diabetic macular edema, ranibizumab, triamcinolon acetat, resistant diabetic macular edema, ıntra-vitreal ınjection*

Diyabetik Maküler Ödemde İntravitreal Ranibizumab Monoterapisi ve İntravitreal Ranibizumab ve İntravitreal Triamsinolon Kombinasyon Tedavisi Sonuçlarımız

Amaç: Diyabetik maküler ödem (DMÖ) tedavisinde intra-vitreal ranibizumab (IVR) monoterapisi ve IVR+intra-vitreal triamsinolon (IVTA) kombinasyon tedavisinin görme keskinliği (GK) ve santral foveal kalınlık (SFK) üzerindeki etkilerini araştırmak.

Gereç ve Yöntemler: Klinik olarak anlamlı DMÖ olan 37 hastanın 52 gözü çalışmaya dahil edildi. Tüm hastalara başlangıçta intra-vitreal yolla 0.5 mg / 0.05 ml ranibizumab uygulandı. 2 ranibizumab enjeksiyonunu takiben yeterli yanıt alınamayan olgulara IVR+IVTA kombinasyon tedavisi uygulandı. Görme keskinliği ve SFK değerleri enjeksiyondan önce ve enjeksiyondan 1, 3 ve 6 ay sonra karşılaştırıldı.

Bulgular: Enjeksiyondan önce ortalama görme keskinliği 0.68±0.42 logMAR iken. Birinci ve üçüncü aylarda görme keskinliğinde enjeksiyon öncesi değerlere göre istatistiksel olarak anlamlı bir artış saptandı (p<0.05). Görme keskinliği altıncı ayda da artmasına rağmen, gruplar arasındaki fark istatistiksel olarak anlamlı değildi (p>0.05). Enjeksiyondan önce ortalama SFK değeri 557.4±157.7 µm idi. Enjeksiyon öncesi SFK ile karşılaştırıldığında 1, 3 ve 6. ayların SFK değerlerinde istatistiksel olarak anlamlı bir azalma saptandı (p<0.05). IVR ve IVR+IVTA kombinasyon tedavisi uygulanan hastalar 6 aylık sonuçlarla karşılaştırıldığında, ortalama GK sırasıyla 0.60±0.41 logMar ve 0.58±0.38 logMar olarak bulunmuştur; ortalama SFK değerleri sırasıyla 419.35±205.5 µm ve 487.0±215.5 µm olarak bulundu. İki grup arasında istatistiksel olarak anlamlı bir fark gözlenmedi (p>0.05).

Sonuç: IVR+IVTA kombinasyon tedavisi, intra-vitreal ranibizumab monoterapisi ile birlikte dirençli DMÖ olgularında alternatif bir yöntem olabilir.

Anahtar Kelimeler: *Diyabetik maküler ödem, ranibizumab, triamsinolon asetat, dirençli diyabetik maküler ödem, intravitreal enjeksiyon*

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Introduction

Diabetes mellitus (DM) is among the main chronic diseases worldwide with an estimated prevalence of 8.5% in 2014 while it was 4.7% in 1980 (1). Diabetic macular edema (DME) is the most important cause of decreased vision in diabetic patients and may be seen at every stage of diabetic retinopathy (2). Focal DME develops from impaired vascular permeability as the result of diabetic micro-vascular changes, exudative leakages from micro-aneursyms and localized capillaries, and diffuse DME develops from widespread capillary leakage as the result of diffuse impairment of blood-retina barrier (3, 4).

In DME treatment, capillary permeability is reduced via VEGF inhibition by intra-vitreal injections and inhibition of many inflammatory mediators by steroid injections. Frequently mono-therapy is applied for treatment. However combination therapies are also applied. Various studies are available in literature about combination therapy of IVB+IVTA and its effectiveness (5-8).

In the present study, we aimed to investigate the influences of IVR and IVR+IVTA on VA and CFT in DME patients followed up in our clinic.

Materials and Methods

Research and Publication Ethics: This study was approved by the Recep Tayyip Erdoğan University Local Review Board and Ethics Committee (Date:03.09.2020 No:2020/192). The research was adhered to the tenets of the Declaration of Helsinki, and detailed written informed consent was taken before each individual's participation in the study.

A total of 52 eyes of 37 patients who were applied intra-vitreal anti-VEGF injection for treatment of DME in Rize Training and Research Hospital between January 2011 and January 2013 were included in the study. Data were obtained from hospital data management system.

Inclusion criteria were as follows: Having clinically significant DME according to ETDRS classification, CFT>300 µm on optic coherence tomography (OCT); absence of vitreo-macular traction, history of cataract surgery, Nd:YAG laser capsulotomy and vitreo-retinal surgery, panretinal photo-coagulation within the recent 6 months; absence of other ocular pathologies which cause macular edema (Age related macular degeneration (AMD), epi-retinal membrane, uveitis, retinal vein stenosis etc.), absence of ischemic maculopathy; absence of pathologies that could influence visual acuity except DME like cataract, corneal opacity, glaucoma; not being pregnant and absence of renal failure. The patients who had regularly come to their controls and who had been followed up for at least 6 months were included in the study.

Detailed systemic and ophthalmic anamnesis was obtained before the injection. Best corrected visual acuity (BCVA) of all patients was evaluated with Snellen table and recorded as logMAR. Bio-microscopic anterior segment and fundus examinations were done. Fundus fluorosceine angiography (FFA) and color fundus photograph were obtained, macular thickness was recorded with the optic coherence tomography (OCT) (Zeiss Cirrus-400) device. Visual acuity at months 1, 3 and 6 after the injection and central foveal thickness (CFT) of the patients were recorded. Internal medicine consultation was made for plasma glucose regulation and systemic hypertension control.

All intra-vitreal injections were made in the operating room. After the topical anesthesia done with proparacaine HCl 0.5% (Alcaine, Alcon), eyelashes and eyelids were washed with povidone iodine solution, intra-ocular space was sterilized with 5% povidone iodine solution or 3 min after sterile eyelid retractor had been inserted. Afterwards eye surface was washed with sterile saline solution. 3.5 mm periphery of the limbus was marked with compass at the upper temporal and intra-vitreal injections were applied vertically to mid-vitreus. A short pressure was applied mildly at injection point with a cotton applicator just after pulling the needle back for prevention of drug or vitreus leakage and sub-conjunctival hemorrhage. Topical moxifloxacin was applied five times daily for one week.

Intra-vitreal ranibizumab (Lucentis®, Genetech, Inc, South San Francisco, California, USA) injection was applied at the dose of 0.5 mg/0.05 ml during the first two months. Patients were called for monthly controls. Data were recorded at months 1, 3 and 6. Re-injection was planned for the patients whose DME continued (CFT>300 µm) and whose visual acuity did not increase. Combination therapy of IVR (0.5 mg/0.05 ml ranibizumab)+IVTA (2 mg/0.05 ml triamcinolon acetonid) (Kenacort-A 40 mg/ml, Bristol-Myers Squibb Co, Princeton, NJ) was applied to the patients whose CFT did not change and visual acuity did not increase following 2 ranibizumab injection with one month interval beginning from the third month.

Data were recorded to SPSS 20.0 statistical package program and descriptive statistics were done for grouping variables and evaluating associations between them. Normality analyses between groups were done with Shapiro Wilk or Kolmogorov Smirnov tests. Wilcoxon test was performed for evaluating the pre and post injection visual acuity and central foveal thicknesses. Mann Whitney U test with Bonferronni correction was used for pairwise comparisons. For multiple group analysis Friedman test was performed. A P value of <0.05 was accepted as statistically significant.

Results

A total of 52 eyes of 37 patients of whom 51.3% (n=19) were females and 48.6% (n=18) were males were included in the study. Mean age of the patients was 60.71±9.2 years (range; 33-76 years), mean age of the females was 61.3±6.8 years and mean age of the males was 61.0±10.8 years. A statistically significant difference was not detected between mean ages according to gender (p=0.410).

All patients were in DM type 2 group. Ten (27%) patients had proliferative diabetic retinopathy (DRP), 27 (72.9%) had non-proliferative DRP. While 16 patients (43.2%) had bilateral DME, 21 patients (56.7%) had unilateral DME.

While mean VA was 0.68±0.42 logMAR (range; 0.10-1.60 logMAR) before the injection, it was found to be 0.54±0.42 logMar (range 0.1-1.6 logMAR) at the first month after the injection; 0.58±0.44 logMar (range; 0.1-1.9 logMAR) at the third month after the injection and 0.59±0.40 logMar (range; 0.1-1.4 logMAR) at the sixth month after the injection for all cases (Figure 1). A statistically significant increase was detected in VA at 1st as compared to pre-injection values (p=0.006).

Although VA increased also at 3th and 6th month injections, the difference was not statistically significant (p=0.152, p=0.537 respectively) (Tablo 1).

While mean CFT was 554.9±150.7 µm (range; 300 - 811 µm) before the injection, it was found to be 359.7±154.5 µm at 1st month; 449.8±202.8 µm at 3rd month and 448.2±207.3 µm (range; 129-957 µm) at 6th month (Figure 2). A decrease was detected in CFT at post-treatment 1,3 and 6. months as compared to pre-operative values (Figure 3). All these reductions in CFT were statistically significant (p<0.001). Group comparisons were shown at the Table 2.

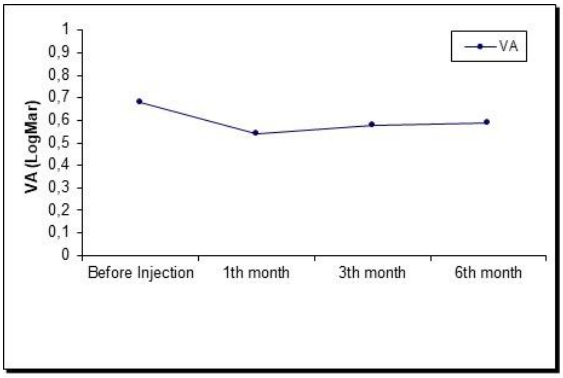

Figure 1. Visual acuity changes of all patients before and after treatment (LogMar).

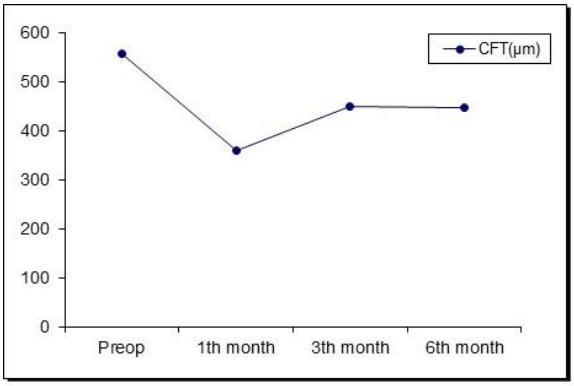

Figure 2. Central foveal thickness (CFT) changes of all patients before and after treatment.

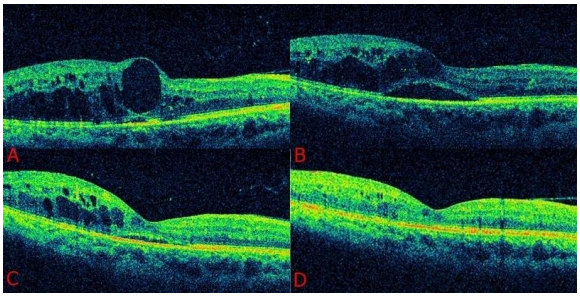

Figure 3. A) OCT photography of a patient with diabetic macular edema before intravitreal injection. **B)** OCT photography of the same patient one month after intravitreal injection. **C)** OCT photography of the same patient 3 months after intravitreal injection. **D)** OCT photography of the same patient 6 months after intravitreal injection.

Combination therapy (IVR+IVTA) was applied to 16 eyes (30.7%) of which VA did not increase and DME did not regress following two consecutive ranibizumab treatments. While mean VA at 6th month was 0.60 ± 0.45 logMar (range; 0.1–1.60) in the patients who were applied only IVR, it was 0.58±0.38 logMar (range; 0.1–1.10) in the patients who were applied combination therapy (Figure 4). The difference was not statistically significant (p=0.439).

A significant difference could not be found between the visual acuities on months 1, 3 and 6 (Table 3) A significant decrease was detected at the first month as compared to month 3 and 6 values when CFT values were compared (p<0.001, p=0.001, respectively). While mean CFT was 419.35±205.5 µm (range; 129-880 µm) at 6th month in patients who underwent only IVR, this value was 487.0±215.5 µm (range; 134-957 µm) in patients who were applied IVR+IVTA combination therapy (Figure 5). The difference was not statistically significant (Table 3).

During follow up period, 3 patients (5.7%) were applied focal LFK and 5 patients (9.6%) were applied PRP. One patient underwent uncomplicated cataract surgery. Complications related with intra-vitreal injections were observed in no patents.

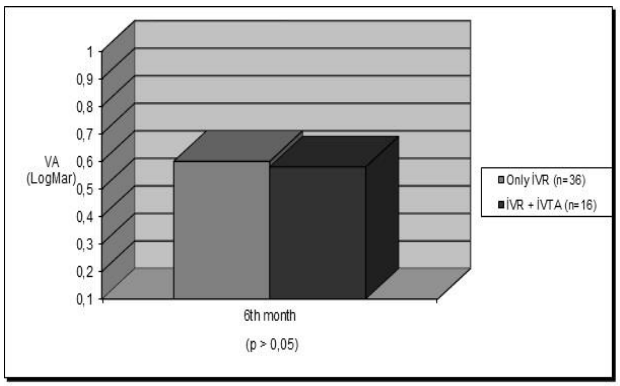

Figure 4. Comparison of visual acuity at the 6th month of treatment of patients with and without combined therapy

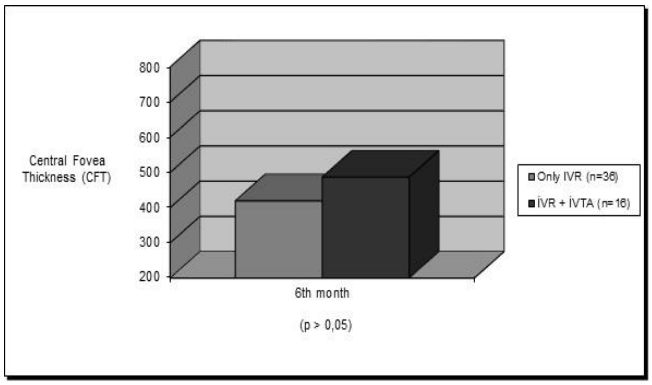

Figure 5. Comparison of **c**entral foveal thickness (CFT) at the 6th month of treatment of patients with and without combined therapy

Table 1. Visual acuities and central foveal thicknesses before injections, after first month, after third months and after sixth months

	Number	Mean	Std. Deviation	Range	Minimum	Maximum
Visual Acuities (Logmar)						
Before injection	52	0,68	0,42	1,50	0,10	1,60
First Month	51	0,54	0,42	1,50	0,10	1,60
Third Month	42	0,58	0,44	1,80	0,10	1,90
Sixth Month	37	0,62	0,38	1,30	0,10	1,40
Central Foveal Thicknesses (Micrometers)						
Before injection	52	554,96	150,74	511,00	300,00	811,00
First Month	52	359,71	154,59	657,00	134,00	791,00
Third Month	44	449,80	202,89	825,00	100,00	925,00
Sixth Month	39	448,21	207,04	828,00	129,00	957,00

Table 2. Comparions of central foveal thicknesses between groups before injection, at the first month, 3rd month and 6 th months.

	Z Values	p Values
Central Foveal Thickness Comparisons		
Before injection- 1 st Month	-5,896	0,001
Before injection- 3 rd Month	-3,069	0,002
Before injection- 6 st Month	-2,568	0,01
First Month- 3 rd Month	-2,474	0,013
First Month- 6 th Month	-3,028	0,002
Third Month- 6 th Mont	-0,966	0,334

Wilcoxon Signed Ranks Test.

Table.3. Visual acuities and central foveal thicknesses of combination therapy (IVR+IVTA) applied patients and intravitreal ranibizumab applied patients before injections, after first month, after third months and after sixth months and their comparisons.

	Combination Therapy (IVR+IVTA) Applied Patients					Intravitreal Ranibizumab Applied Patients					p Values
	Number	Mean	Std. Deviation	Min.	Max.	Number	Mean	Std. Deviation	Min.	Max.	
Visual Acuities (Logmar)											
Before injection	16	0,48	0,29	0,10	1,10	36	0,78	0,44	0,10	1,60	0,022
First Month	15	0,45	0,35	0,10	1,10	36	0,60	0,45	0,10	1,60	0,256
Third Month	15	0,60	0,49	0,10	1,90	27	0,62	0,41	0,10	1,60	0,681
Sixth Month	15	0,59	0,37	0,20	1,10	22	0,65	0,39	0,10	1,40	0,743
Central Foveal Thicknesses (Micrometers)											
Before injection	16	597,94	175,62	300,00	810,00	36	535,86	136,65	300,00	811,00	0,129
First Month	16	387,44	167,28	160,00	791,00	36	347,39	149,41	134,00	715,00	0,367
Third Month	16	518,13	226,34	160,00	925,00	28	410,75	180,96	100,00	838,00	0,100
Sixth Month	16	489,69	208,53	134,00	957,00	23	419,35	205,59	129,00	880,00	0,291

Mann-Whitney U test

Discussion

Diabetic macular edema is the most important cause of impaired vision in diabetic patients and may be seen in every stage of DRP (9). Focal DME develops as the result of exudative leakage from micro-aneursyms and localized capillaries due to impaired vascular permeability resulting from diabetic micro-vascular changes and diffuse DME develops as the result of widespread capillary leakage due to diffuse impairment of blood-retina barrier (10, 11).

The standard treatment options accepted for DME-related impaired vision include a strict plasma glucose regulation, hypertension control and laser photocoagulation (LP) treatment (12, 13). The ETDRS study has reported that LP treatment decreased moderate visual impairment in the ratio of 50% in clinically significant macular edema (14) . Novel pharmacologic and vitreo-retinal surgical treatment options have been developed due to the potential side effects and complications of LP treatment in DME. An

ample amount of studies are available about the use and effectiveness of IVTA in DME that does not recover despite laser treatment (5, 15). However high ratio of cataract and increased intra-ocular pressure (IOP) due to IVTA has restricted its use in DME (16-19). That type of side effects have not been reported with anti-VEGFs that developed as an alternative treatment.

Levels of VEGF in vitreous and humor aqueous increase directly proportionally with the increase in DME (20). The two main pathologies responsible for impaired vision in diabetic retinopathy (DR) are DME that developed from the increased retinal vascular permeability and retinal neo-vascularization. VEGF which is a potent angiogenic stimulator and vascular permeability factor plays a role in both of these pathologies. Pharmacologic inhibition of VEGF has become an actual treatment method in ocular diseases in which blood-retinal barrier is impaired, vascular permeability increases and neo-vascularization is seen. The signaling pathway which is triggered with VEGF's binding to trans-membrane thyrosine kinase receptors on endothelial cells may be inhibited at many levels and the effectiveness of VEGF may be prevented (21).

The effectiveness of ranibizumab in YBMD has been proven with MARINA and ANCHOR studies and it is widely used in this field (22, 23). Many studies have also been performed about its effectiveness in DME.

In READ-1 study (Ranibizumab for Edema of the Macula in Diabetes: Phase-1),10 patients with chronic DME were applied 0.5 mg ranibizumab on months 1,2,4 and 6 following the first dose and evaluated with VA and CFT measurements on month 7. Mean 85% reduction (from 503 µm to 257 µm) was detected in CFT and mean 12.3 letters of increase was detected in VA. A strong correlation was detected between the thinning in CFT and the increase in VA. A mild increase was detected in systemic blood pressure of the patients following the injections however no thrombo-embolic complications were encountered (24, 25).

READ-2 (Ranibizumab for Edema of the Macula in Diabetes: Phase-2) is a prospective, randomized, multi-center study. In the study, 126 patients who had DME were allocated to three groups as 0.5 mg ranibizumab, focal/grid laser treatment and their combination. Group 1 (0.5 mg ranibizumab) consisted of 42 patients and treated on months 1,3,5 following the first injection. Group 2 was also consisted of 42 patients and received focal/grid treatment at the beginning and re-applied laser if CFT was>250 µm at the third month. Group 3 also consisted of 42 patients who received 0.5 mg ranibizumab at the beginning and at the third month of the study, and they also received focal/grid laser treatment. Evaluations were done at 6th month and VA increase was found to be better in the patents who were applied only ranibizumab as compared to the one who were applied laser treatment. In addition, CFT decrease was found to be 50%, 33% and 45% in the groups, respectively. So ranibizumab alone was found to be more effective at 6th month assessments (25).

In 2 year of long-term outcomes of READ 2 study have revealed that ranibizumab mono-therapy increased VA and decreased CFT however injection frequency could be reduced with its combination with focal laser treatment (25).

In RESOLVE (Safety and Efficacy of Ranibizumab in Diabetic Macular Edema with Center Involvement) study, the influences of ranibzumab on DME and VA were investigated until 12 months in 151 patients who had clinically significant macular edema. The study was a randomized, double-blinded, multi-center, phase 2 study. The patients whose CFT was>300 µm were allocated to three groups as intra-vitreal 0.3 mg or 0.5 mg ranibizumab groups and control group, ranbizumab was administered during the first 3 months and continued until 9 months when required following the first 3 months. The researchers were given two additional authorities in order to apply two fold of ranibizumab dose (0.6 mg or 1 mg) monthly and to apply laser treatment when required if CFT>300 µm or the thinning in CFT<50 µm one month later. When 12 month outcomes were evaluated, while VA increased 11.8 and 8.8 letters, respectively in 0.3 mg and 0.5 mg groups, 1.4 letter loss was seen in control group. Levels of CFT decreased mean 194.2±135.1 µm in ranibizumab groups and 48.4±153.4 µm in control group. In the study, a significant improvement was observed in VA and CFT in the groups treated with ranibizumab as compared to control group. Safety profile of ranibizumab was found to be similar with that of YBMD. Systemic hypertension developed in 8.8% and 10.2% of the patients, respectively and thrombo-embolic events were seen in the ratio of 2.9% and 4.1%, respectively (26).

DRCR.net (The Diabetic Retinopathy Clinical Research Network) study was conducted on 854 eyes. Patients were allocated to 4 groups as 0.5 mg ranibizumab and early laser (1 weeks), 0.5 mg ranibizumab and late laser (24 weeks later), laser + sham injection and IVTA+early laser (1 weeks). Ranibizumab was found to be superior to only laser or IVTA+laser combination when applied with early or late laser at 12th month evaluation. On year 2 evaluations, the increase in vision was seen to stop in laser group although CFT thinning continued and VA at the end of 2 years was seen not to be significantly different than the end of first year. In IVTA+laser group, although both CFT decrease and VA increase continued within the first year, both CFT increased again and visual impairment occurred within the second year. On the other hand, the decrease in CFT and the increase in VA that were achieved within the first year were also preserved in the second year. According to these results, the outcomes in ranibizumab + laser group were shown to be superior to the outcomes of the other groups, in other words, laser alone and IVTA+ laser groups. The increase in IOP and frequency of cataract development were found to be significantly higher in patients who were applied IVTA as compared to the patients who were applied ranibizumab (27, 28).

The designs of RISE and RIDE studies are similar. They are randomized, double-blinded and multi-center phase 3 studies based on the comparison of 24 and 36 month outcomes of 0.3 mg, 0.5 mg ranibizumab and control groups. In 24 month outcomes, while no difference was found between monthly ranibizumab treatments of 0.3 mg, 0.5 mg, a significant difference was detected when compared to control group with regard to VA improvement and CFT. Sham injections were discontinued after 24 months, and 36 month outcomes were reported. It was seen that VA improvement and CFT thinning continued also at 36th month however final VA was seen not to reach these values in the group that sham injections discontinued (29).

In our study, IVR injection caused a significant increase VA and a significant decrease in CFT, similarly with all of these studies.

Intra-vitreal bevacizumab (IVB) injection that is applied as non-indication use due to its similar molecular structure to ranibizumab was shown to be effective in YBMD and DME and retinal vein occlusions (30-32).

Combination therapies are also used for pharmacologic treatment of DME. Many studies are available about IVB+IVTA combination therapy in DME (7, 8, 32, 33).

In the randomized, three-arm clinical study of Lim et al. conducted on 111 eyes with DME revealed that while the patients in IVB+IVTA combination therapy and IVT mono--therapy group had better VA and thinner CFT as compared to IVB mono-therapy group at 6 weeks and 3 months, all groups were similar with regard to VA and CFT at 12th month (8, 33).

In the study of Faghihi et al. conducted on 130 eyes with DME, IVB or IVB+IVTA combination therapy provided more thinning in CFT as compared to standard laser therapy. However the response to therapy had a shorter effect in IVB mono-therapy group (7).

In the study of Tao et al. investigating IVTA use in DME, the authors reported that IVTA had lost its leadership after the introduction of bevacizumab and ranibizumab in clinical use however kept its place in combination therapy due to biological effectiveness and wide therapeutic spectrum (34) .

Differently from the other studies, we applied IVR+IVTA combination therapy in patients who were considered to have resistant macular edema (whose CFT did not change and VA did not improve after 2 IVR injections with one month interval) in our study. The increase in VA and the thinning in CFT at 6 months were close to each other in patients in IVR+IVTA combination therapy group and IVR mono-therapy group ($p<0.05$). The results of our study were similar with those of the studies which applied combination therapy in DME (32, 33). We applied IVTA in half dose (2 mg) and did not detect an increase in IOP and cataract incidence, probably due to this.

The weaknesses of our study are small number of the patients in combination therapy group, short duration of follow up (6 months) and not considering macular and pan-retinal LFKs. Our applying combination therapy only to the resistant patients who do not respond to mono-therapy and comparing the results with mono-therapy group may seem as a bias however our aim was to show that reasonable outcomes could be obtained with combination therapy in resistant DME. The similarity between the increase in VA and the decrease in CFT obtained with combination steroid injections in resistant DME and obtained with mono-therapy may suggest that combination therapies may also be a good alternative. Steroid administration in reduced doses as in our study may be protective with regard to steroid side effects however further studies are required.

In conclusion, as shown in many clinical studies, intra-vitreal anti-VEGF use in DME increases VA and decreases CFT better as compared to laser mono-therapy and IVTA and Focal/grid laser treatment which is known as the gold standard in DME treatment leaves its place to intra-vitreal anti-VEGF medications. In our study, ranibizumab which is an anti-VEGF with a proven effectiveness in DME was used. Mean 1.71±0.84 (range; 1-6) injections were applied during 6 months and a statistically significant decrease was detected in CFT at 1,3 and 6th months as compared to pre-operative values ($p<0.05$). A statistically significant increase was detected in VA at 1st and 3rd months as compared to pre-injection values ($P<0.05$). While VA also improved at 6th month, the difference was not statistically significant ($p>0.05$). Differently from the previous studies, IVR+IVTA combination therapy was applied in patients who were considered to have resistant DME (whose CFT did not change and VA did not improve following 2 ranbizumab injections with one month interval). The increase in VA and the thinning in CFT at 6th month were found to be similar between combination therapy group and IVR mono-therapy group. Although the effectiveness of anti-VEGF and steroids was proven with many clinical studies, a standard treatment protocol has not been developed yet. Combination therapies may be considered as an alternative in DME cases however further studies are required.

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