

Comparison of the efficacy of aflibercept and ranibizumab after a 3-month loading dose in patients with diabetic macular edema

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Ethics Committee Approval

For the present study, the approval of the Ethics
Committee of Karabük University was obtained
(decision no:2020/248, dated:09/06/2020).
All procedures in this study involving human
participants were performed in accordance with
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amendments.

Conflict of Interest

No conflict of interest was declared by the
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Abstract

Background/Aim: Diabetic macular edema (DME) is the main cause of visual loss in diabetic patients. Aflibercept and ranibizumab are among the most commonly used intravitreal agents in the DME. This study aims to compare the short-term anatomic and functional results of aflibercept and ranibizumab in the treatment of DME.

Methods: This retrospective cohort study included newly diagnosed and treatment-naïve DME patients. The patients were administered intravitreal aflibercept (IVA) or intravitreal ranibizumab (IVR) as a loading dose throughout 3 months. Pre-treatment and 1- and 3-month examinations were made of best corrected visual acuity (BCVA) and central macular thickness (CMT). After the treatment, the patients were classified in the 3rd month as those with good or poor response according to the early anatomic response. A good response to the treatment was considered the formation of foveal contour and full recovery of macular edema. Patients where macular edema was not fully resolved and/or foveal contour had not formed were classified as having poor response. Later, IVA and IVR were compared with each other in terms of response to treatment.

Results: Evaluation was made of 67 eyes of 54 patients, comprising 31 (57.4%) females and 23 (42.6%) males with a mean age of 62.7 (7.3) years (range, 46-78 years). IVA was applied to 33 (49.3%) eyes and IVR to 34 (50.7%) eyes. In the IVA group, BCVA was determined as 0.75 (0.39) LogMAR pre-treatment, 0.53 (0.37) LogMAR at 1 month and 0.38 (0.30) LogMAR at 3 months ($P<0.001$ for each). CMT was measured as 400 (82) μm pre-treatment, 349 (95) μm at 1 month and 313 (79) μm at 3 months ($P<0.001$ for each). In the IVR group, BCVA was determined as 0.71 (0.34) LogMAR pre-treatment, 0.52 (0.34) LogMAR at 1 month and 0.39 (0.30) LogMAR at 3 months ($P<0.001$ for each). CMT was measured as 426 (92) μm pre-treatment, 365 (74) μm at 1 month and 323 (60) μm at 3 months ($P<0.001$ for each). A good response to treatment was determined in 24 eyes (72.7%) in the IVA group, and in 18 eyes (52.9%) in the IVR group. Although a good response to treatment was achieved at a higher rate in the IVA group, the difference was not statistically significant ($P=0.09$).

Conclusion: Both visual and anatomic success was achieved with a 3-month loading dose in both the IVA and IVR groups. No statistically significant superiority was determined of one drug over the other in the 3-month period.

Keywords: Aflibercept, Ranibizumab, Diabetic macular edema

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that develops when sufficient insulin is not produced in the pancreas or the produced insulin is not used effectively [1]. In 2013, the number of diabetic patients was 382 million worldwide and this is predicted to increase by 55% to reach 592 million by 2035 [2].

Chronic hyperglycemia that emerges in diabetes causes microvascular and macrovascular complications. Diabetic retinopathy (DR) is the most frequently seen microvascular complication [3]. Diabetic macular edema (DME) is a reason for sight loss in DM and can be seen at any stage of DR [4]. In a prevalence study based on optic coherence tomography (OCT), Acan et al. reported the prevalence of DME as 15.3% in 443 diabetic patients [5]. Various methods have been described for DME treatment, the most frequently used of which are laser photocoagulation, intravitreal steroids, and anti-vascular endothelial growth factor injections (VEGF) [6-8]. Aflibercept and ranibizumab are anti-VEGF drugs approved for use in DME treatment [3, 7-10]. Anti-VEGF agents are currently preferred as the first treatment option in DME treatment [11]. In the Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol T study, aflibercept was shown to provide better visual results than both the bevacizumab and ranibizumab group in a 1-year follow-up period, especially in patients with low visual acuity (<0.4) [12].

The aim of this study was to compare the short-term anatomic and functional results of aflibercept and ranibizumab in the treatment of DME.

Materials and methods

For the present study, the approval of the Ethics Committee of Karabuk University was obtained (decision no:2020/248, dated:09/06/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

This retrospective study included patients diagnosed with DME and treated with intravitreal aflibercept (IVA) and intravitreal ranibizumab (IVR) in the Ophthalmology Clinic of Karabuk University Training and Research Hospital between 01.09.2017 and 31.05.2018. Informed consent was obtained from all patients before starting treatment.

The patients included were those who were newly diagnosed with DME, had not previously received any treatment, received loading doses of aflibercept or ranibizumab for the first 3 months, and completed a minimum follow-up period of 4 months. Patients were excluded if they had any retinal disease other than DME, or if they had previously undergone any intravitreal injection or laser photocoagulation treatment.

The data related to patient age, gender, lens status, drugs used, best corrected visual acuity (BCVA) and central macular thickness (CMT) at pre-treatment, 1 month and 3 months were examined from the patient records. At each follow-up examination, BCVA was measured with a projection chart at 4 meters, intraocular pressure (IOP) was measured with an air tonometer (Canon, TX-20P, Canon, Japan), CMT was measured with optical coherence tomography (OCT) (Cirrus HD-OCT 4000, Carl Zeiss Meditec, Germany) and detailed biomicroscopic

and fundus examinations were performed after dilation. Fundus fluorescein angiography (Canon Cx-1, Canon, Japan) was only used pre-treatment, but was repeated in cases where patient sight deteriorated for no known reason during the follow-up period. OCT was used to determine DME and measure CMT. In diagnosis, CMT >300µm indicated DME. The CMT values were calculated from the mean thickness of the neurosensory retina in a central area of 1mm diameter, using the OCT mapping software.

Following treatment, the patients were classified at the end of 3 months as good or poor according to the early anatomic response. A good response to the treatment was accepted as the formation of foveal contour and full recovery of macular edema. Patients where macular edema was not fully resolved and/or foveal contour had not formed were classified as poor response. The groups were compared in terms of the response to IVA and IVR treatments.

All injections were administered in the operating theatre under sterile conditions. The eyelids and surrounding areas were wiped with a sterile gauze pad soaked in 10% povidone-iodine. Anesthesia of topical proparacaine hydrochloride was applied then the eye was washed with 5% povidone-iodine. The injections were administered from the supero-temporal quadrant, with a 27-gauge needle, at 4mm behind the limbus in phakic eyes, and at 3.5mm in pseudophakic eyes in 3 doses at 1-month intervals as 2mg/0.05ml Aflibercept (Eylea, Regeneron, New York, USA and Bayer Health Care, Berlin, Germany) or 0.5 mg/0.05 ml Ranibizumab (Lucentis, Genentech Inc., San Francisco, USA). To prevent leakage after the injection, a sterile cotton swab stick was pressed onto the entry site then Vigamox (moxifloxacin) drops were instilled in the eye and the drops were continued for 7 days at a dose of 4 drops per day. Patients were instructed to return to the hospital immediately without waiting for the follow-up appointment if they experienced any reduced vision, eye pain, or any new symptom.

The primary endpoint of this study was defined as the rate of good anatomic responses in the 3rd month after 3 loading dose injections of Aflibercept and Ranibizumab.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn.21.0 software (SPSS Inc, Chicago, IL, USA). The visual acuity values were converted to the logarithmic value for minimum resolution (LogMAR) for statistical analysis. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. Numerical variables were stated as mean (standard deviation), and categorical variables, as number and percentage. For the comparison of three groups of numerical variables with normal distribution, One-Way variance analysis (ANOVA) was used for repeated measurements, and Bonferroni correction was applied if the result was significant. The Independent Samples t-test was used in the comparisons of numerical variables between two groups. The changes in BCVA and CMT from pre-treatment to 3 months were evaluated in each treatment group using the Dependent Samples t-test. Categorical variables were compared using the Chi-square test. A value of $P < 0.05$ was considered statistically significant.

Results

Evaluation was made of 67 eyes of 54 patients, comprising 31 (57.4%) females and 23 (42.6%) males with a mean age of 62.7 (7.3) years (range, 46-78 years). IVA was applied to 33 (49.3%) eyes, and IVR to 34 (50.7%) eyes. The general characteristics of the groups are summarized in Table 1.

In both the IVA and IVR groups, a statistically significant increase was determined in mean BCVA at the end of 1 and 3 months compared to the baseline values ($P < 0.001$ for all) (Table 2). The mean gain in BCVA at the end of the 3rd month was 3.6 in the IVA group and 3.1 in the IVR group. No statistically significant difference was determined between the groups with respect to the improvement in mean BCVA ($P = 0.50$).

In both the IVA and IVR groups, a statistically significant decrease was determined in mean CMT at the end of 1 and 3 months compared to the baseline values ($P < 0.001$ for all) (Table 2). The mean decrease in CMT at the end of the 3rd month was 86 μ m in the IVA group and 102 μ m in the IVR group ($P = 0.92$).

A good response to treatment was determined in 24 eyes (72.7%) in the IVA group, and in 18 eyes (52.9%) in the IVR group, which were similar ($P = 0.09$).

Among a total of 201 injections administered, no endophthalmitis was observed in any of the patients.

Table 1: General characteristics of the patients before the injections

	IVR	IVA	P-value *
Age (years)	63.8 (8.3)	61.1 (6.5)	0.300
Right/left	18/16	16/17	0.904
Preoperative BCVA (LogMAR)	0.71 (0.34)	0.75 (0.39)	0.548
Preoperative CMT (μ m)	426 (92)	400 (82)	0.579

* Independent Student's t-test, Chi-square test, CMT: Central macular thickness, BCVA: Best corrected visual acuity

Table 2: Changes in the BCVA and CMT values of the patients from pre-treatment to 1 month and 3 months after the injections

	Pre-treatment	IVR			P-value *	Pre-treatment	IVA			P-value *
		1 month	3 months	P-value			1 month	3 months	P-value	
CMT (μ m)	426 (92)	365 (74)	323 (60)	<0.001	400 (82)	349 (95)	313 (79)	<0.001		
BCVA (LogMAR)	0.71 (0.34)	0.52 (0.34)	0.39 (0.30)	<0.001	0.75 (0.39)	0.53 (0.37)	0.38 (0.30)	<0.001		

* repeated measures variance analysis, CMT: Central macular thickness, BCVA: Best corrected visual acuity

Discussion

Diabetic macular edema (DME) is the most common cause of sight loss in diabetic patients and is a leading cause of blindness in the working-age population in developed countries. Although DME can be seen at any stage of diabetic retinopathy (DR), as the duration of DM increases, so does the frequency of DME with advanced stages of DR [13]. However, corneal damage may occur in patients with DME [14].

For many years, focal and grid laser application was the gold standard in the treatment of DME [15]. However, as laser treatment does not increase visual acuity sufficiently and because of potential complications, new treatments have been researched. Compared to laser treatment, anti-VEGF agents are more successful in increasing visual acuity and reducing macular thickness and so have become the current standard treatment for DME [16].

Previous studies have found that VEGF is the main angiogenic factor responsible for the development of DR and DME, and a correlation has been shown between the VEGF level and retinopathy activity [17-19]. The VEGF family is formed of

VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor (PlGF). Ranibizumab is a humanized monoclonal antibody, which is produced by recombinant Escherichia coli, and is effective against all isoforms of VEGF-A. It was the first agent approved by the FDA for DME treatment. Aflibercept is a 115 kDa-weighted, recombinant fusion protein, formed with fusion of the Fc part of human immunoglobulin G1 and the extracellular parts of VEGFR-1 and VEGFR-2. VEGF-A binds to VEGF-B and PlGF with high affinity.

There are several studies in literature about the efficacy of IVA in DME treatment. In the DA VINCI, which was a phase II study, greater improvements were observed at the end of 24 weeks in the IVA groups than in the laser group [20]. In VIVID and VISTA, which were multicenter, randomized, double-blind phase 3 studies, the administration of IVA was statistically significantly superior to laser treatment in terms of anatomic and functional success [21]. Demir and Kutluturk [22] reported IVA is an effective and safe treatment agent for both improving BCVA and decreasing CMT in DME patients.

In a retrospective study by Erden et al. [23], BCVA changed from 0.54 (0.28) LogMAR pre-treatment to 0.32 (0.37) LogMAR after 3 months of 2mg IVA loading. The CMT of these patients decreased from 415 (88) μ m pre-treatment to 277 (54) μ m at the end of 3 months. According to these results, the administration of IVA was effective in the treatment of DME with a 3-month loading dose.

In the current study, similar results to those of previous studies were obtained in the IVA group with statistically significant improvements in BCVA and CMT after a 3-month loading dose.

There are several studies in literature showing that IVR administration is effective in the treatment of DME. In the phase II Resolve study, the administration of IVR was more effective than sham injection at the end of 1 year [24]. In the phase III Restore study, it was concluded that IVR treatment alone or combined with laser provided better results than laser treatment alone [25].

In a retrospective study by Erden et al. [23], BCVA improved from 0.58 (0.28) LogMAR pre-treatment to 0.32 (0.26) LogMAR at the end of 3 months as a result of 3 months of 0.5mg IVR loading. In these patients, CMT decreased from 406 (82) μ m pre-treatment to 303 (60) μ m at the end of 3 months. Nowacka et al. [26] applied 0.5mg IVR for 3 months to 17 eyes of 17 patients with DME, and reported BCVA as 0.62 (0.28) LogMAR pre-treatment and 0.4 (0.22) LogMAR after 3 months, and a decrease in CMT from 542 (136) μ m pre-treatment to 325 (68) μ m at the end of 3 months. According to these results, the administration of IVR was effective in the treatment of DME with a 3-month loading dose.

In the current study, similar results to those of previous studies were obtained in the IVR group with statistically significant improvements in BCVA and CMT after a 3-month loading dose.

In the DRCT-net protocol T study, which was designed to compare anti-VEGF drugs currently used in DME treatment, the efficacy and reliability of aflibercept, ranibizumab and bevacizumab were examined in the treatment of DME, which can lead to sight loss through involvement of the central retina. At the

end of one year, an increase in BCVA was determined with a mean of 13.3 letters in the patients treated with aflibercept, 11.2 letters with ranibizumab, and 9.7 letters with bevacizumab (aflibercept – bevacizumab $P < 0.001$, aflibercept – ranibizumab $P = 0.03$). When the first visual acuity score was ≥ 69 letters, the mean increase in BCVA score was 8.0 letters for aflibercept, 8.3 letters for ranibizumab, and 7.5 letters for bevacizumab, and no statistically significant difference was determined between the groups. However, when the first visual acuity score was < 69 letters, the mean increase in BCVA score was 18.9 letters for aflibercept, 14.2 letters for ranibizumab, and 11.8 letters for bevacizumab. According to these results, in the group with lower initial visual acuity, aflibercept treatment was significantly more successful in the first year than ranibizumab and bevacizumab [12].

When the 2-year results of the Protocol T study were examined, the BCVA increase was determined as 12.8 letters for aflibercept, 12.3 letters for ranibizumab, and 10 letters for bevacizumab (aflibercept - bevacizumab: $P = 0.02$, aflibercept - ranibizumab: $P = 0.47$, ranibizumab - bevacizumab: $P = 0.11$). From these results it was seen that at the end of 2 years, ranibizumab treatment was able to reach the same treatment results as aflibercept, but bevacizumab did not show the same success. When the patients were separated into groups according to the initial visual acuity, there was no statistically significant difference between the drugs in the patient group with BCVA ≥ 69 letters, while for those with a score of < 69 letters, no difference was determined between aflibercept and ranibizumab. However, aflibercept treatment was significantly more successful than bevacizumab [10].

In a study by Erden et al. [23], treatment-naïve DME patients were separated into two groups and IVA was applied to one group and IVR to the other. At the end of 3 months, there was no statistically significant difference between IVA and IVR in terms of both BCVA gain and CMT decrease. In a prospective study by Fouda et al. [27], 70 patients were separated into two groups, and received 2mg/0.05 ml IVA per month or 0.5mg/0.05ml IVR per month. At the end of 3 months, the improvement in BCVA on the Snellen chart was 1.8 rows in the IVA group and 1.5 rows in the IVR group. The decrease in CMT at the end of 3 months was reported as 95 μ m in the IVA group and 77 μ m in the IVR group. In this study, no significant difference was found between the two groups in terms of efficiency in the short term.

In current study, similar results were obtained with previous studies. No statistically significant difference was found between the two groups in terms of BCVA gain and CMT decrease with the 3-month loading dose.

Limitations

The limitations of our study include its retrospective and single-centered nature, and small number of patients.

Conclusion

The results of this study demonstrated that both visual and anatomical success can be achieved with a 3-month loading dose of both IVA and IVR. No statistically significant superiority was determined of one drug over the other in the 3-month period. Although the rate of patients with a good response to treatment was higher in the IVA group than in the IVR group, the difference was not statistically significant.

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