Comparison of Efficacy of Intravitreal Aflibercept and Ranibizumab in Treatment-naive Diabetic Macular Edema

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Abstract

Objective: The purpose of this study was to compare the efficacy of two different intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents in two treatment-naive and statistically equal cohorts of diabetic macular edema patients.

Methods: In this retrospective study, 81 eyes of 64 treatment-naive diabetic macular edema (DME) patients were enrolled. Patients were divided into two groups and both groups were treated [37 eyes with intravitreal 0.5 mg ranibizumab (IVR) and 44 eyes with intravitreal 2 mg aflibercept (IVA)] with three consecutive injections at intervals of one month. All patients underwent a detailed eye examination including optic coherence tomography and best corrected visual acuity (BCVA; Snellen), biomicroscopy, fundoscopy and applanation tonometry at preoperative, 1st, 2nd and 3rd month. BCVA values were converted into logarithm of the minimum angle of resolution (logMAR) for statistical analyses. Data were evaluated with SPSS 25.0.

Results: Mean BCVA (logMAR) increased from 0.58±0.28 to 0.43±0.29, 0.39±0.25 and 0.32±0.26 (p=0.001, p<0.001, p<0.001) in the IVR group and from 0.54±0.28 to 0.41±0.34, 0.43±0.39 and to 0.32±0.37 (p=0.004, p<0.001, p<0.001) in the IVA group. Mean central macular thickness (CMT) decreased from 406±82 µm to 345±65 µm (1st month), 332±83 µm (2nd month) and finally to 303±60 µm (3rd month) (p<0.001) in the IVR group and from 415±88 µm to 328±79 µm, 297±54 µm and finally to 277±54 µm (p<0.001) in the IVA group, respectively. There was no significant difference between the groups in terms of BCVA (p>0.05). In the subgroup analysis, CMT gain in patients with moderate DME (CMT ≤385 µm) was found significantly better in the IVA group compared to the IVR group (1st month: 36.9 vs. 83.6, 2nd month: 36.2 vs. 106.3, 3rd month: 36.7 vs. 125.1; p<0.05).

Conclusion: Both anti-VEGFs were equally effective in visual outcomes. Compared to ranibizumab, aflibercept has a rapid and superior therapeutic effect in anatomical results, especially in moderate DME cases.

Keywords: Aflibercept, anti-vascular endothelial growth factor, diabetic macular edema, ranibizumab

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of visual impairment in the diabetic population (1). According to a meta-analysis of 22,896 diabetic patients, the prevalence of center-involving DME was 6.81% (2). Historically, several interventional therapies such as focal/grid laser photocoagulation, intravitreal/pericircular corticosteroids (triamcinolone acetone etc.) or pars plana vitrectomy have proven to be effective in the treatment of focal or diffuse DME. However, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs with safe and effective profile have been considered as first-line therapy for DME in the last decade. Recently, the results of Protocol T trial of Diabetic Retinopathy Clinical Research Network (DRCR. net) - the most discussed comparison of three anti-VEGF drugs (ranibizumab, aflibercept on-label and bevacizumab off-label) - were published, including the post-hoc analysis in several publications (3,4). In this study, we aimed to compare the efficacy of two on-label anti-VEGFs in two comparable, treatment-naive diabetic edema cohorts under real-life conditions.

METHODS

This study was conducted at the Istanbul Okmeydanı Training and Research Hospital, Clinic of Ophthalmology. The study was approved by Clinical Research Ethics Committee of Okmeydanı Training and Research Hospital and adhered to the principles of the Declaration of Helsinki. Initially, medical records and
RESULTS

A total of 81 eyes of 64 treatment-naive DME patients were included in the study. Forty-four eyes of 36 patients were taken into the IVA cohort and 37 eyes of 28 patients were taken into the IVR cohort. There was no significant difference between the groups in terms of age, gender, serum HbA1c levels, duration of diabetes, baseline BCVA and CMT values (Table 1). The IVR group was treated with 0.5 mg IVR (Lucentis®, Genentech) for three consecutive months and the IVA cohort was given 2.0 mg IVA (EYLEA®, Regeneron Pharmaceuticals, Inc.) for three consecutive months.

Functional Outcome

Mean baseline BCVA (logMAR) improved in the IVR group from 0.58±0.28 to 0.43±0.29 (1st month, p=0.001), 0.39±0.25 (2nd month, p<0.001) and 0.32±0.26 (3rd month, p<0.001), respectively. In the IVR group, the mean BCVA also increased substantially from 0.54±0.28 to 0.41±0.34 (1st month, p=0.004), 0.43±0.39 (2nd month, p=0.023) and to 0.32±0.37 (3rd month, p<0.001). Regarding the total study population, the intergroup comparison between cohorts revealed no significant difference in monthly visits at follow-up (multivariate analysis, p=0.84) (Figure 1). In the subgroup analysis including eyes with low baseline BCVA (Snellen; VA <0.3), the intergroup comparison of IVR (n=18) and IVA (n=18) cohorts was insignificant at each visit (p=0.61) (Figure 2a). In the higher baseline BCVA (Snellen; VA ≥0.3) subgroup, although visual gain trends tended to be slightly superior in IVA cohort at the 1st month visit, statistical comparison of IVR (n=19) and IVA (n=26) cohorts revealed no significant difference (p=0.85) (Figure 2b).

Statistical Analysis

Statistical analyses were performed using SPSS software version 25. The variables were investigated for normal distribution via visual (histogram) and analytical (Kolmogorov-Smirnov) methods. Visual acuities in Snellen (decimal) were converted to the logarithm of the minimum angle of resolution (logMAR) for statistical purposes. Independent t-test and Mann-Whitney U test were preferred to compare baseline demographical and clinical features between groups. Analysis were conducted in the entire study population and in two anatomical and visual subgroups of both treatment cohorts, based on baseline best corrected visual acuity BCVA levels and CMT values with the cut-off value of 0.3 Snellen lines and 385 µm. Repeated ANOVA measures was used to investigate the change in BCVA and CMT over time. A p value of less than 0.05 was considered to be statistically significant.

Table 1. Baseline demographical and clinical features of both cohorts

<table>
<thead>
<tr>
<th></th>
<th>IVR (n=28*, n=37**)</th>
<th>IVA (n=36*, n=44**)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.9±7.9</td>
<td>58.3±9.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Gender</td>
<td>M: 61.5%; F: 38.5%</td>
<td>M: 62.3%; F: 37.7%</td>
<td>0.94</td>
</tr>
<tr>
<td>Duration of DM (year)</td>
<td>11.2±2.3</td>
<td>12.3±2.2</td>
<td>0.64</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.38±0.5</td>
<td>7.34±0.6</td>
<td>0.75</td>
</tr>
<tr>
<td>PreCMT</td>
<td>406±82 µm</td>
<td>415±88 µm</td>
<td>0.62</td>
</tr>
<tr>
<td>PreBCVA (logMAR)</td>
<td>0.58±0.28</td>
<td>0.54±0.28</td>
<td>0.58</td>
</tr>
</tbody>
</table>

IVR: Intravitreal ranibizumab, IVA: Intravitreal aflibercept, M: Male; F: Female; DM: Diabetes mellitus, PreCMT: Pre-treatment central macular thickness; PreBCVA: Pre-treatment best corrected visual acuity, HbA1c: Glycosylated hemoglobin A, logMAR: Logarithm of the minimum angle of resolution

*Number of patients, **Number of study eyes
In the IVA group, the baseline mean CMT also decreased significantly from 415±88 µm to 328±79 µm (1st month), 297±54 µm (2nd month) and finally to 277±54 µm (3rd month) (p<0.001), respectively. The intergroup comparison of monthly CMT values showed a significant superiority of IVA group at the 2nd month visit (p=0.03) (Figure 3). Additionally, the anatomical gain comparisons between IVR and IVA groups (60 vs. 87 µm; 73 vs. 118 µm; 103 vs. 137 µm) indicated a general superiority in the IVA group over IVR group, which was statistically significant at 2nd month visit (p=0.09; p=0.03; p=0.07, respectively). In the subgroup analysis of anatomical evaluation, we divided the total study group into severe and moderate DME subgroups according to the cut-off value (385 µm; median value). In severe DME (CMT >385 µm; IVR n=18; IVA n=22 ) cases, the mean CMT value in the IVR cohort decreased from 472±64 µm to 371±81 µm, to 340±94 µm and finally to 313±78 µm, respectively. In the IVA group, the mean CMT decreased from 483±74 µm to 362±92 µm, to 320±56 µm and finally to 291±61 µm, respectively. The intergroup comparison of CMT reduction in this severe DME subgroup revealed no significance (p=0.42) (Figure 4a). On the other hand, the mean CMT in IVR group with moderate DME decreased significantly from 343±28 µm to 321±32 µm, to 323±72 µm and finally to 292±34 µm at 3rd month visit (p<0.01). However, in the IVA group, a rapid and greater CMT reduction (from 346±24 µm to 294±45 µm, to 273±41 µm and to 264±45 µm; p<0.001) was observed. The comparison of both anti-VEGF agents in moderate DME cases revealed a statistically significant difference in favor of IVA group during the follow-up (p=0.03), starting from the 1st month visit (Figure 4b).

DISCUSSION

The major cause of visual loss in diabetic population with non-proliferative retinopathy is center-involving DME. The anti-VEGF drugs have dominated clinicians’ treatment approach over the
last decade, with promising results and relative safety starting with the off-label use of bevacizumab (5). Following the usage of bevacizumab, two on-label agents, ranibizumab and aflibercept, were introduced into our daily practice with superior results from their representative trials (6,7). In addition, anti-VEGF agents have proved to be superior to conventional therapies. Monotherapy with IVR showed better clinical results than conventional laser photocoagulation (8). Corticosteroids such as dexamethasone has well-known potential risks such as cataract progression and glaucoma, so they have a limited indication in the treatment of DME patients (9). Therefore, clinicians prefer anti-VEGFs as the first-line therapy for this common clinical entity (10).

The on-going debate about which anti-VEGF would be recommended in each individual case has often been dependent on the clinician’s experience in daily practice, local administrative regulations of the countries or financial issues. Recently, the comparative clinical trial Protocol T of DRCR.net reported first and second year results (3,4). While the overall visual results of the first year did not reveal any statistical difference between these three anti-VEGFs, aflibercept was significantly superior compared to ranibizumab (p=0.0003) and bevacizumab (p=0.0001) in the lower baseline BCVA (≤20/50) subgroup (3).

Regarding the anatomical results of the whole study population, the greatest decrease in mean CMT was found in the aflibercept group (169±139 µm vs. 147±134 µm vs. 101±121 µm) at the end of the 1st year. However, for the 2nd year results of this trial, the ranibizumab group caught up on the aflibercept group both in visual and anatomical gains (12.8 letters vs. 12.3 letters;
171±141 µm vs. +149±141 µm), both on-label anti-VEGFs remained their superiority over bevacizumab (4). The Protocol T results partially supported the theoretical superiority aflibercept in visual gain, especially in low-vision cases. Therefore, we tried to compare ranibizumab and aflibercept in different baseline BCVA subgroups and aimed to find any differences in a particular clinical situation. Contrary to Protocol T findings in low baseline BCVA subgroup analysis, the IVA group in our study did not differ from the IVR group at any particular visit. Both anti-VEGF groups reached comparable functional endpoints at the final visit, such as the final result of the 2nd year of the Protocol T trial.

The reason for better efficacy of aflibercept over the 1st year results of the Protocol T trial may be due to its broader pharmacological features. In contrast to the antibody-based VEGF binding mechanism of ranibizumab and bevacizumab, aflibercept blocks the specific binding domains of the VEGF receptor (VEGFR)-1 and the VEGFR-2 (11). Aflibercept binds all isoforms of VEGF-A like the other two anti-VEGFs, additionally it also binds VEGF-B and placental growth factor, and the intermediate size of the molecule (110 kD, compared to 48 kD for ranibizumab and 148 kD for bevacizumab) create a potential monthly intravitreal activity that theoretically exceeds both ranibizumab and bevacizumab (12). This long-lasting effect is also reflected in some practical clinical reports. In their study comparing ranibizumab and aflibercept, Shimizu et al. (13) concluded that visual improvement in DME patients following consecutive intravitreal injections lasted significantly longer in aflibercept group than in ranibizumab group (6 vs. 3 months). In the IVA arm of their report, a subgroup of the patients had previous IVR treatment for DME. They found that IVA treatment did not improve the visual acuity further in previously treated IVR subgroup, but that the mean CMT decreased equally in both subgroups with or without prior IVR history.

In conclusion, our results demonstrated that ranibizumab and aflibercept were equally effective in visual prognoses of treatment-naive center-involving DME cases. Aflibercept distinguished itself in anatomical results, especially in moderate DME subgroups. The finding might be due to the multiple-sided inhibiting mechanism of aflibercept. Further real-world experience reports are needed for comprehensive evaluation of our conclusions.
Acknowledgements

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Ethics

Ethics Committee Approval: The ethics committee approval was obtained from the local ethical committee at Istanbul Okmeydani Training and Research Hospital (approval number: 1116).

Informed Consent: Written informed consent was obtained from each participant of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions


Conflict of Interest: The authors of this study do not have any conflict of interest

Financial Disclosure: No financial support was received for this study.

REFERENCES