ORIGINAL ARTICLE

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

● Burak Erden[1], ● Akın Çakır[1], ● Selim Bölükbaşı[1], ● Ali Cihat Aslan[2], ● Mustafa Nuri Elçioğlu[1]

[1]İstanbul Okmeydanı Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey
[2]Urfa State Hospital, Clinic of Ophthalmology, Şanlıurfa, Turkey

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=0.023, 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: 3nd 72.7 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/periocular corticosteroids (triamcinolone acetonide 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 İstanbul 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

Eur Arch Med Res 2019;35(3):170-4

Erden et al. Comparison of Aflibercept and Ranibizumab in Diabetic Macular Edema

electronic data of 121 eyes of 99 treatment-naive DME patients who underwent administration of three consecutive intravitreal anti-VEGF injections at a loading phase between August 2017 and November 2018 at our retina department were reviewed retrospectively. Our inclusion criteria were center-involving DME with a central macular thickness (CMT) >280 μm, proper administration of three consecutive monthly intravitreal anti-VEGF injections, availability of serum glycosylated hemoglobin A (HbA1C) levels in the peri-treatment period (±3 months at the initiation of the treatment), patients older than 18 years and diagnosis of type 2 diabetes mellitus (DM). Patients with type 1 DM, coexisting vitreoretinal interface pathologies such as epiretinal membrane, taut hyaloid or vitreomacular traction, any stage of proliferative diabetic retinopathy detected in baseline fluoresceine ongiography (FA), any intraocular surgery 6 months prior to the study, and ophthalmic comorbidities such as vein occlusion or glaucoma were excluded. According to our exclusion/inclusion criteria, 99 eyes of 82 patients were eligible for pre-enrollment evaluation. Further, we excluded 18 eyes of 18 patients from both intravitreal aflibercept (IVA) and intravitreal ranibizumab (IVR) groups to obtain statistically indifferent cohorts in terms of diabetes duration, serum HbA1C levels, gender distribution and age. Finally, 81 eyes of 64 patients were included in our retrospective study. All patients underwent a comprehensive ophthalmologic examination, including Snellen visual acuity testing, slit-lamp biomicroscopy, dilated fundus examination, Goldmann applanation tonometry, optical coherence tomography (OCT) examination with standard deviation-OCT (Spectralis; Heidelberg Engineering Inc, Heidelberg, Germany) by two certified technicians at all visits and FA at the pre-treatment period.

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.

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 of 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 IVA 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).

Table 1. Baseline demographical and clinical features of both cohorts

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

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
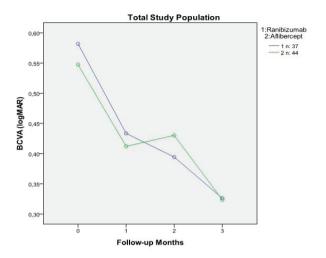*Number of patients, **Number of study eyes

Erden et al. Comparison of Aflibercept and Ranibizumab in Diabetic Macular Edema

Eur Arch Med Res 2019;35(3):170-4

Figure 1. The visual gain comparison in the total study group

logMAR: Logarithm of the minimum angle of resolution, BCVA: Best corrected visual acuity
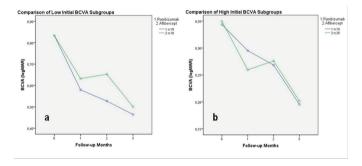

Figure 2. a) Comparison of intravitreal aflibercept and intravitreal ranibizumab groups in visual prognosis in low baseline best corrected visual acuity subgroup b) and in high baseline best corrected visual acuity subgroup

logMAR: Logarithm of the minimum angle of resolution, BCVA: Best corrected visual acuity
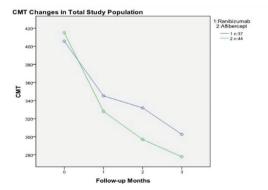

Figure 3. The regression of macular edema in the total study group
CMT: Central macular thickness

Anatomical Outcome

The mean CMT was significantly reduced in the IVR group 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), respectively.

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
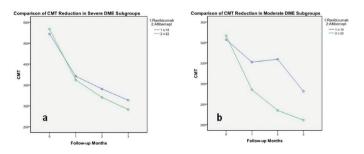

Figure 4. a) The subgroup analyses of central macular thickness reduction in response to intravitreal aflibercept and intravitreal ranibizumab treatments in severe macular edema cases b) and in moderate macular edema cases
CMT: Central macular thickness

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. We believe this finding actually points to the additional anatomical efficacy of aflibercept. In the subgroup analysis of anatomical results of our study, IVA and IVR were found to be comparatively effective in the total study population, except for the 2nd month visit, and in the severe DME subgroup, but IVA proved to be significantly more effective in moderate DME cases. As a general rule, the more severe the macular edema, the more dramatically the CMT will decrease as a response to an effective treatment modality, however, the fact being significantly more effective in reducing the mean CMT of moderate DME cases clearly indicated the superior anatomical efficacy of aflibercept, probably due to its VEGF-trap character. The major limitations of this current study were clearly its retrospective nature and the absence of any randomization. We tried to eliminate the biases arising from its design by reviewing a large number of patient data and enrolling only eligible patients in the IVR and IVA groups to conduct two comparable treatment arms. Unlike representative clinical trials of anti-VEGFs (14,15), where patients get a much higher amount (7-12 times/year) of regular injections, real life based reports such as the Pride Study (16) reveal a much lesser frequency of intravitreal treatments (4 IVR injections/18 months). This fact clearly emphasizes the difference between randomized clinical trials and evidence findings in the real world.

CONCLUSION

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.

Erden et al. Comparison of Aflibercept and Ranibizumab in Diabetic Macular Edema

Eur Arch Med Res 2019;35(3):170-4

Ethics

Ethics Committee Approval: The ethics commitee approval was obtained from the local ethical commitee at İstanbul Okmeydanı Training and Research Hospital (approval number: 1116).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., A.Ç., A.C.A., S.B., Concept: B.E., A.Ç., S.B., Design: B.E., A.Ç., M.N.E., Data Collection or Processing: A.C.A., B.E., S.B., A.Ç., Analysis or Interpretation: B.E., A.Ç., Literature Search: B.E., A.Ç., A.C.A., S.B., Writing: B.E., A.Ç., S.B.

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

REFERENCES

1. O'Doherty M, Dooley I, Hickey-Dwyer M. Interventions for diabetic macular oedema: a systematic review of the literature. Br J Ophthalmol 2008;92:1581-90.

2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.

3. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372:1193-203.

4. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology 2016;123:1351-9.

5. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina 2006;26:999-1005.

6. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789-801.

7. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology 2012;119:1658-65.

8. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615-25.

9. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904-14.

10. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017;237:185-222.

11. Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002;99:11393-8.

12. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667-8.

13. Shimizu N, Oshitari T, Tatsumi T, Takatsuna Y, Arai M, Sato E, et al. Comparisons of Efficacy of Intravitreal Aflibercept and Ranibizumab in Eyes with Diabetic Macular Edema. Biomed Res Int 2017;2017:1747108.

14. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology 2015;122:2044-52.

15. Ishibashi T, Li X, Koh A, Lai TY, Lee FL, Lee WK, et al. The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema. Ophthalmology 2015;122:1402-15.

16. Menchini U, Bandello F, De Angelis V, Ricci F, Bonavia L, Viola F, et al. Ranibizumab for Visual Impairment due to Diabetic Macular Edema: Real-World Evidence in the Italian Population (PRIDE Study). J Ophthalmol 2015;2015:324841.