Comparison of outcomes between intravitreal ranibizumab and intravitreal aflibercept for diabetic macular edema with “Treat-and-Extend” regimen

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Abstract

Background To compare the effectiveness of intravitreal ranibizumab (IVR) and aflibercept (IVA) with the Treat-and-Extend (TAE) regimen for diabetic macular edema (DME).

Patients and methods Thirteen eyes received an intravitreal injection of 0.5 mg ranibizumab (mean age, 70.9±6.0 years) and 13 eyes received 2 mg aflibercept (65.9±8.6 years). After 3 consecutive monthly injections, they received additional injections with the TAE regimen. The changes in the best-corrected visual acuity (BCVA), CRT, and total number of injections were compared.

Results No significant differences were detected in the baseline demographics. The BCVA was significantly improved for both groups; 0.31±0.19 to 0.10±0.12 logMAR units for IVR and 0.41±0.19 to 0.16±0.28 logMAR units for IVA at 24 months (P <0.01). The CRT was significantly reduced in both groups; 440.9±69.3 to 307.5±66.4 μm for IVR and 473.9±71.5 to 317.8±71.2 μm for IVA at 24 months (P <0.01). No significant differences were detected in the improvements of the BCVA and reduction in the CRT between them. The total number injections were significant fewer for the IVA group (11.0±1.2) than the IVR group (12.0±1.0) at 24 months (P =0.02).

Conclusion The results showed that the TAE regimen was effective. The IVA group required fewer injections to attain the same improvements.

Background

Diabetic macular edema (DME) is a leading cause of blindness in working age individuals [1,2], and many factors are related to its onset. Especially, vascular endothelial growth factor (VEGF) associated with vascular proliferation and hyperpermeability. Its suppression is effective in resolving the DME and many randomized clinical trials have shown that intravitreal anti-VEGF injections are the first-line treatment for DME [3–7]. Although the number of injections will be reduced over the years, the results of randomized control studies have shown that it requires repeat injections or frequent visits. So, other flexible regimens are often used, and because of the risk-benefit balance the optimal regimen still needs to be established.

Treatment as needed or *pro re nata* (PRN) regimen is frequently used. The timing of the injection is mainly determined by retinal thickness as assessed by optical coherence tomography (OCT) [8, 9], and it has been reported that patients receive fewer injections with this regimen than the monthly injections. The PRN regimen is also used for other retinal diseases including age-related macular degeneration (AMD). In fact, 75.0% of the Japanese ophthalmologists prefer the PRN regimen for DME during the maintenance phase [10]. Previous studies have shown that the PRN regimen for AMD had similar visual outcomes as the monthly injection regimen, and comparable outcomes could be achieved with fewer injections [11–15]. However, the PRN regimen is inconvenient because it requires frequent visits. In addition, the HORIZON trial found that non-adherence to the monthly monitoring led to a loss of the benefits of the previous treatments [16].

Much attention has been recently given to the Treat-and-Extend (TAE) regimen, and its main goal was to minimize the number of injections and patient visits. The TAE regimen consisted of a loading phase injection and a maintenance phase in which the injection interval is determined by the disease activity. Many studies have reported on the effectiveness of TAE regimen for AMD [17–21]. A meta-analysis of 26,360 patients from 42 real-world observational studies of intravitreal ranibizumab (IVR) showed that the TAE regimen resulted in better visual outcomes with fewer visits compared to the PRN regimen for AMD at 2 years [22]. These results indicated that an individualized treatment and follow-up schedule is possible for each patient with the TAE regimen. Relevant to this study, the TAE regimen with IVR has been also reported to be effective for DME [23–25].

At present, three anti-VEGF agents, bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), ranibizumab (Lucentis, Genentech), and aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA) have been approved and used to treat DME. However, it had not been definitively determined whether there are differences in their effectiveness. The Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol-T study reported that aflibercept was more effective especially in patients with initially poor vision as long as a strict PRN regimen was followed [26]. However, there is no study that compared the effectiveness of IVR and intravitreal aflibercept (IVA) using the TAE regimen for DME. Thus, the purpose of this study was to compare the effectiveness of IVR and IVA applied with the TAE regimen for the treatment of DME.

Patients And Method

Patients who had been diagnosed with DME and had received IVR or IVA using the TAE regimen for more than 24 months without any additional treatment were studied. All of the patients were examined in the Department of Ophthalmology of the Mie University Hospital between April 2014 to November 2018. The procedures used in this study were approved by the Institutional Ethics Review Board of the Mie University Hospital (#702), and the study was registered at http://www.umin.ac.jp (UMIN ID 000033728). The procedures adhered to the tenets of the Declaration of Helsinki and a signed informed consent was obtained from all patients.

Each patient had a comprehensive ophthalmological examination including measurements of the best-corrected visual acuity (BCVA) and intraocular pressure, examination of the anterior segment by slit-lamp biomicroscopy, examination of the fundus by indirect ophthalmoscopy, and the macular structure by spectral-domain optical coherence tomography (SD-OCT).

The inclusion criteria were; presence of DME, age at least 20 years, and BCVA pretreatment of 20/320 or better. The diagnosis of DME was made by the clinical findings, fluorescein angiography, and a central retina thickness (CRT) greater than 250 μm in the SD-OCT images. The exclusion criteria were; prior ocular surgery within 6 months, macular laser photocoagulation, and intravitreal or sub-tenon injections of steroids within 3 months of the beginning of this study. In addition, eyes with ocular inflammation, drusen, severe proliferative diabetic retinopathy, retinal hemorrhage which involved the intra- or subfoveal

spaces, an epiretinal membrane, any history of pars plana vitrectomy, glaucoma, and media opacities that significantly affected the BCVA were excluded. Patients with uncontrolled systemic medical conditions or history of thromboembolic events were also excluded. Diabetes control was evaluated by the HbA1c levels (normal range:4.6–6.2%), and renal dysfunction was evaluated by the estimated glomerular filtration rate (eGFR; normal range: 60–120 ml/min/m^2).

Intravitreal anti-VEGF injections

Intravitreal anti-VEGF injections were performed under local subconjunctival or topical anesthesia. Each patient received 0.5 mg of ranibizumab (IVR group) or 2 mg of aflibercept (IVA group) intravitreally with a 30-gauge needle that was inserted 4 mm posterior to the corneal limbus under sterile conditions. All patients received topical levofloxacin hydrate, (1.5% Cravit ophthalmic solution) for 1 week after the injection.

All patients were given 3 consecutive monthly injections, the loading phase, as described in detail [24, 27], and they continued the therapies with IVR or IVA injections with a modified TAE regimen.

Modified-TAE regimen for DME

In the maintenance phase, the follow-up injection intervals were applied according to a modified-TAE regimen as described in detail [24], and the initial treatment interval was set at 8 weeks. The injection interval was extended by 2 weeks if the CRT was <350 μm at 2 consecutive examinations, and the injection interval was shortened by 2 weeks if the CRT was >350 μm or increased by more than 20% of the baseline value.

Measurements of best-corrected visual acuity (BCVA)

The BCVA was measured with a Landolt chart at every visit. The decimal BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units for the statistical analyses.

Optical coherence tomography (OCT)

The measurements of the CRT were made on the images recorded by a Heidelberg Spectralis OCT instrument (Heidelberg Engineering Inc, Heidelberg, Germany). For qualitative and quantitative analyses of the OCT images, the fast macula protocol was used to obtain the images with an automatic real time mean value of 9 which acquired 25 horizontal lines consisting of 1024 A-scans per line. The CRT was defined as the thickness between the internal limiting membrane and the retinal pigment epithelium at the fovea, and the value was automatically calculated from the center subfield of the macular thickness map using the bundled software.

Statistical Analyses

The results are presented as the means ± standard deviations (SDs). Paired *t* tests were used to determine the significance of the differences between corresponding pairs in the two groups. Two-way repeated measures ANOVA and post-hoc *t* tests with Bonferroni's corrections were used to determine the significance of the changes in the BCVA and CRT. Two-tailed *P* values of <0.05 were significant. The statistical evaluations were performed by Statcel 4 Statistical Program (Statcel; OMC, Saitama, Japan).

Results

This was a retrospective, single-center study of 26 eyes of 26 consecutive patients. Thirteen DME patients received IVR, and 13 DME patients received IVA. The clinical characteristics of the patients are summarized in Table 1. No significant differences in the baseline values were found between the two groups; the mean age of the IVR group was 70.9 ± 6.0 years and that for the IVA group II was 65.9 ± 8.6 years, The HbA1c levels was 7.6 ± 1.6% for the IVR group and 7.4 ± 1.8% for the IVA group, and the eGFR level was 87.1 ± 16.1 ml/min/m^2 for the IVR group and 71.0 ± 21.7 ml/min/m^2 for the IVA group. There were no related ocular complications including intraocular pressure elevations, infections, or adverse systemic events.

The mean baseline BCVA were 0.31 ± 0.19 logMAR units in the IVR group and 0.41 ± 0.19 logMAR units for the IVA group (*P* >0.05; Table 1). The mean baseline CRT was 440.9 ± 69.3 μm for the IVR group and 473.9 ± 71.5 μm for the IVA group (*P* >0.05; Table 1). The BCVA was significantly improved to 0.13 ± 0.16 logMAR units in the IVR group and to 0.24 ± 0.22 logMAR units in the IVA group after the loading phase (Table 2). At 6 months, the BCVA was improved to 0.13 ± 0.11 logMAR units in the IVR group and 0.18 ± 0.18 logMAR units in the IVA Group, and at 12 months, the BCVA was 0.14 ± 0.18 logMAR units for the IVR group I and 0.14 ± 0.17 logMAR units for the IVA group II. At 18 months, the BCVA was 0.10 ± 0.17 logMAR units for the IVR group and 0.17 ± 0.31 logMAR units for the IVA group. The final BCVA at 24 months was significantly improved to 0.10 ± 0.12 logMAR units for the IVR group and 0.16 ± 0.28 logMAR units for the IVA group ($P = 1.29 \times 10^{-9}$).

The CRT was also significantly improved during the observation period (Table 2); 334.7 ± 99.3 μm for the IVR group and 348.7 ± 53.5 μm for the IVA group after the loading phase, 352.2 ± 95.1 μm for the IVR group and 333.09 ± 82.0 μm for the IVA group at 6 months, 311.8 ± 60.9 μm for the IVR group and 332.9 ± 72.6 μm for IVA group at 12 months, 310.2 ± 58.2 μm for for the IVR group and 299.9 ± 62.6 μm for the IVA group at 18 months. The mean final CRT at 24 months was significantly improved to 307.5 ± 66.4 μm for the IVR group and 317.8 ± 71.2 μm for the IVA group ($P = 3.55 \times 10^{-9}$). No significant difference was observed between the groups.

The number of injections with the TAE regimen are shown in Figure 1. The mean injection numbers at 12 months was 7.1 ± 0.3 for the IVR group and 6.5 ± 0.5 for the IVA group (*P* = 0.005, Figure 1a and Table 3). The mean number of injections at 18 months was 9.5 ± 0.8 for the IVR group and 8.8 ± 0.9 for the IVA group (*P* = 0.02, Figure 1b and Table 3). The mean number of injections at 24 months was 12.0 ± 1.0 for the IVR group and 11.0 ± 1.2 for the IVA group (*P* = 0.02, Figure 1c and Table 3). The mean interval

between injections was 12.0 ± 3.4 weeks for the IVR group and 12.2 ± 3.2 weeks for the IVA group with no significant difference (P = 0.90).

Discussion

The results showed that IVR and IVA applied with the TAE regimen resulted in a significant improvement of the BCVA and the CRT in eyes with DME. In addition, there were no significant differences in the degree of improvement of the BCVA and CRT. However, these improvements were accomplished with fewer injections with IVA than with IVR for 24 months.

For eyes with AMD, the TAE regimen required more injections than the PRN regimen but required fewer visits with better visual outcomes [22]. When we compared our results to that of previous studies on DME including those using the TAE regimen, e.g., the RETAIN study and T-REX DME, our results are comparable to them even though the patient background and treatment protocol differed (Table 4). The changes in the mean BCVA and CRT with the TAE regimen appear to be comparable to that with the PRN regimen as in the DRCR.net protocol-T. A fixed injection appears to have better improvements, but it required more injections than that with the PRN or the TAE regimens. On the other hand, the number of injections were fewer with PRN, but the intervals were longer with the TAE regimen. The RETAIN study [23] compared the outcomes of the IVR-TAE regimen with the IVR-PRN regimen, and the results showed that the injection interval could be extended to more than 8 weeks for 70% of the patients. The T-REX DME study [25] compared the monthly IVR treatment group, IVR-TAE group and the IVR-TAE combined with laser group. The results showed that significantly fewer injections were required for both the TAE groups than with the monthly group. Thus, the results of these TAE studies indicated that TAE regimens can reduce the number of injections with comparable outcomes to PRN for DME.

However, there are disadvantages of TAE; 1) it requires frequent injections in the first year and may be an over treatment regimen, 2) difficulty in identifying a stable status during the treatment, 3) increased chance of adverse complications, 4) limited evidence on this regimen, 6) there is no stop criteria, and 7) not all patients can complete the longitude treatments with the TAE regimen [24, 28]. We conclude that even though TAE is effective both with IVR and IVA, we need more consideration for these disadvantages.

Our results showed that the mean number of injections at 24 months was fewer by the TAE regimen than other protocols. The patient visits at 24 months was longer than previous studies using the TAE regimen; 12.1 for IVR and 11.0 for IVA. They were lower than that reported by the RETAIN study (12.4 with IVR) and TREX-DME (18.9 with IVR). In addition, the injection intervals were 12.0 weeks for IVR and 12.2 weeks for IVA at 24 months. They are longer than that of the RETAIN study (9.2 weeks with IVR) and TREX-DME (6.7 weeks with IVR). But it is difficult to compare these results directly because the TAE regimen differed somewhere between the studies. It has been reported that the mean BCVA improvements during anti-VEGF treatment for DME is negatively correlated with the baseline BCVA (ceiling effect), and this may be related to the lower BCVA improvements compared to other prospective studies. Different from the AMD treatment, there is no consensus for the TAE regimen for DME, and this is why such differences occurred

although all of them had better outcomes. Thus, it is still important to establish an optimal TAE regimen for DME.

The DRCR.net protocol-T [26] reported that at one year, IVA was more effective for eyes with poor baseline BCVA but the difference was not significant at 2 years. There are several factors that can explain the differences between the two agents After an intravitreal injection, aflibercept penetrates deeper into the retina than ranibizumab in monkey eyes [29], and the VEGF concentration in the aqueous was suppressed longer after IVA than IVR in monkey eyes [30]. In addition, aflibercept binds not only to VEGF and placenta growth factor but to galectin–1 [31]. Our results showed that the TAE regimen was effective for both IVR / IVA, but IVA required fewer injections than IVR. The DRCR.net protocol-T reported significant differences in eyes with lower baseline BCVA group between IVR and IVA for the BCVA / CRT improvements at 12 months though this difference was not significant at 24 months. These findings indicate that much stronger responses occur during the first 12 months after IVA than IVR. We found a significant fewer injection numbers at 12 months after IVR although no significant difference was found for both BCVA and CRT. This is consistent with the 12-month results of the DCRC.net protocol-T. Because we did not divide the patients by the BCVA at the baseline, we could not find any significant difference in the BCVA and CRT between these agents. Thus, we can conclude that our results were significant for the fewer injection number with IVA. Although the RETAIN and T-REX DME studies reported the usefulness of the TAE regimen for DME, no previous study has shown the difference between IVR and IVA with the TAE regimen. The different molecular properties of these two agents may be the reason for this.

There are some limitations in our study including the small sample size. In addition, we selected a CRT of 350 μm as the main criterion to extend the interval between injections. This is comparable to the TREX-DME criterion of 325 μm. However, the RETAIN study based the extension criterion on the visual acuity. It is known that a thinner CRT does not necessarily indicate a better BCVA because there are some cases whose outer segments of the photoreceptors were already damaged even before the DME was resolved. Such phenomenon is called a paradoxical change between BCVA and CRT for DME [32]. Because we defined the CRT as a standard for treatment extension, this TAE regimen cannot cover those patients with lower CRT with poorer BCVA. It is still not clear which is a better criterion to use. Another limitation was that 6 of the 26 eyes of both groups (23.1%) could not extend the interval to more than 8 weeks. In the RETAIN study, about 30% patients could not extend the interval to more than 8 weeks. These eyes received fixed 8 weeks injections, and this is not precise TAE because it contributed less to patients' benefit. It is also important consider other treatment including sustained steroid agents [33–35] for these cases when the injection interval cannot be extended. Finally, we did not compare our TAE results with the PRN regimen. Although the RETAIN study and T-REX DME reported superiority of the TAE regimen compared to the PRN regimen, it is difficult to argue against the usefulness of PRN regimen. In the real world, we perform extra injections mainly dependent on the complaints of the patients without a strict PRN regimen. So, it is not clear whether a strict PRN regimen works better than TAE regimen, and we need to compare them in the future.

Conclusions

The TAE regimens for DME may be a good option for patients with DME because it will result in good vision and a reduction of the CRT with longer injection intervals. It offers individualized patient management with a reduction in the number of visits and injections which would contribute to better patient care.

Abbreviations

Age-related macular degeneration (AMD), best-corrected visual acuity (BCVA), central retina thickness (CRT), diabetic macular edema (DME), intravitreal aflibercept (IVA), intravitreal ranibizumab (IVR), optical coherence tomography (OCT), *pro re nata* (PRN), spectral-domain optical coherence tomography (SD-OCT), standard deviations (SDs), treat-and-Extend (TAE)vascular endothelial growth factor (VEGF).

Declarations

Ethics approval and consent to participate

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

The procedures used in this study were approved by the Institutional Ethics Review Board of the Mie University Hospital (#702), and the study was registered at http://www.umin.ac.jp (UMIN ID 000033728).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Masahiko Sugimoto have:

[Financial Support] Alcon Pharma and Bayer.

[Other (lecture fee)] Alcon pharma, Kowa Pharma, Senjyu Pharma, Daiichi Yakuhin Sangyo, Bayer, Wakamoto Pharma.

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Authors' contributions

M. S., and M. K. designed the study. M. S. and S. C. contributed to writing the main manuscript text. S. C., T. S., A. I., R. M. and H. M. recruit patients and analyzed data. All authors reviewed the manuscript.

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Disclosure Statement

Masahiko Sugimoto have:

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Figure legends

Figure 1. Number of intravitreal Injections of ranibizumab (IVR) and aflibercept (IVA).

Number of injections for each observation period is shown. The bar graph shows the number of injections at 12 months (a), 18 months (b), and 24 months (c). Data are shown as the percentage of all patients.

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Figures

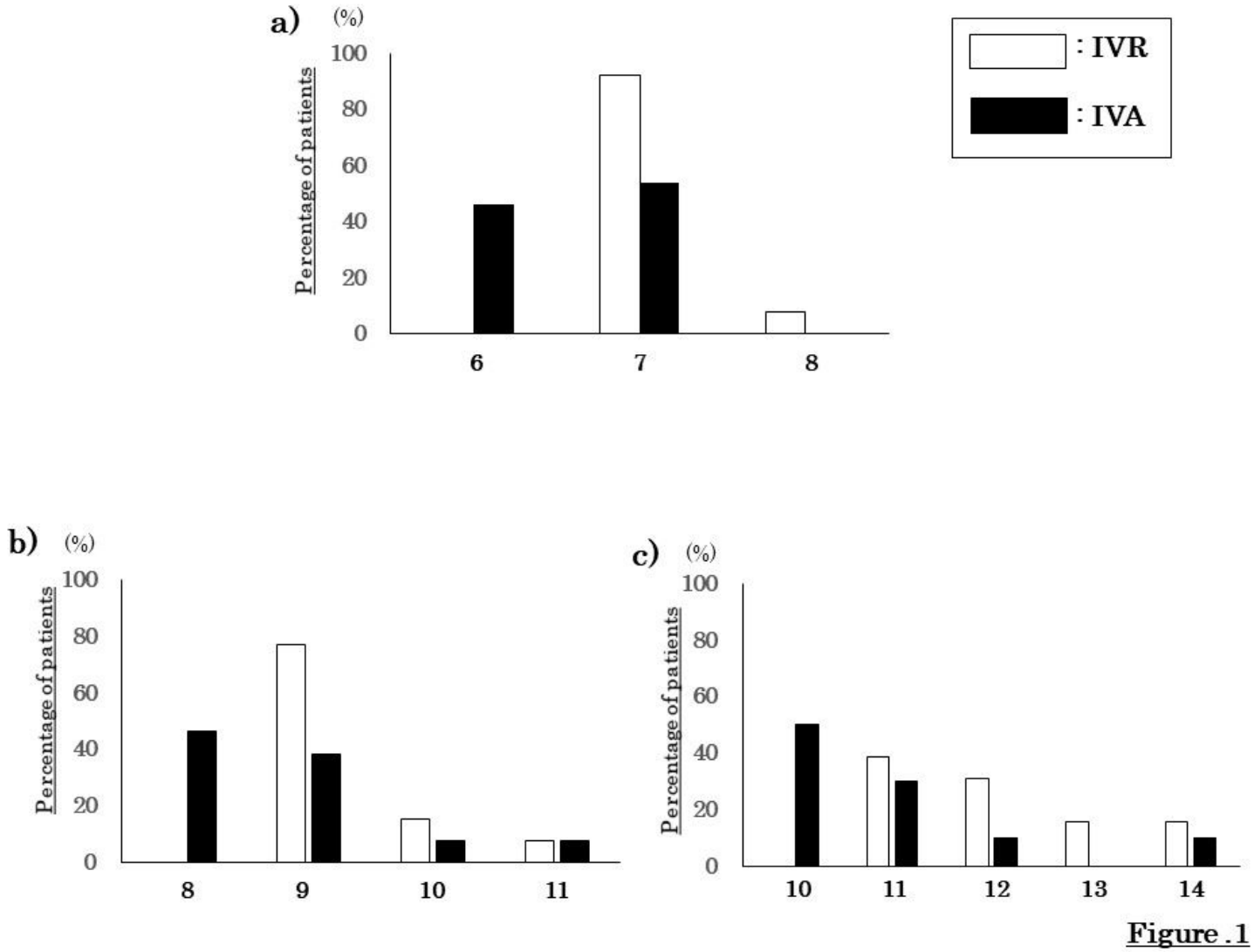

Figure 1

Number of intravitreal Injections of ranibizumab (IVR) and aflibercept (IVA). Number of injections for each observation period is shown. The bar graph shows the number of injections at 12 months (a), 18 months (b), and 24 months (c). Data are shown as the percentage of all patients.