

Short-term outcomes in patients with branch retinal vein occlusion who received intravitreal aflibercept with or without intravitreal ranibizumab

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Purpose: The purpose of this study was to determine the short-term outcomes for patients who received intravitreal aflibercept (IVA) with or without intravitreal ranibizumab (IVR) for macular edema (ME) due to branch retinal vein occlusion (BRVO).

Patients and methods: Patients received IVA for ME due to BRVO. Patients who initially received IVA were defined as the treatment-naïve group and those who were switched from IVR to IVA after ME recurrence were defined as the switching group. Patient outcomes were examined at 1 week and 1 month postinjection.

Results: Both groups comprised 27 eyes from 27 patients. There was a significant decrease in central macular thickness (CMT) at 1 week and 1 month postinjection in both groups. There was also a significant improvement in best-corrected visual acuity (BCVA) at 1 week and 1 month postinjection in the treatment-naïve group and 1 month in the switching group. Younger age was associated with a good BCVA at 1 month postinjection in the switching group, and the absence of epiretinal membrane was associated with a reduction in CMT at 1 month postinjection in the switching group.

Conclusion: IVA is temporarily effective for treating ME due to BRVO regardless of a history of IVR use.

Keywords: BRVO, IVR, IVA, switch

Introduction

Retinal vein occlusion (RVO), which can be classified as central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO), is the second most common type of retinal vascular disease after diabetic retinopathy.^{1,2} RVO can induce a loss of visual acuity due to the presence of macular edema (ME),¹⁻³ current treatments including intravitreal dexamethasone implants, laser treatment, and intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents.³⁻²⁶ Anti-VEGF therapy is widely used for ME due to BRVO, and positive clinical outcomes have been reported,^{3-11,27-29} with numerous studies reporting on the successful use of the VEGF antibody ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA, USA), because ranibizumab use is first covered by insurance as anti-VEGF agents for vitreous injection. After ranibizumab, there have been large treatment studies involving the VEGF inhibitor aflibercept (Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA)²⁸, but only one clinical report has described treatment outcomes of intravitreal aflibercept (IVA) for BRVO.²⁹ There have also been few reports of switching from ranibizumab to aflibercept for the treatment of ME due to CRVO,^{24,25} and none for ME due to BRVO. The short-term outcomes of treatments involving aflibercept and

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switching from ranibizumab to aflibercept for ME due to BRVO were therefore evaluated.

Patients and methods

Ethics

This retrospective study was conducted in accordance with the Declaration of Helsinki. All necessary authorizations were obtained from the Institutional Review Board of the Juntendo University Urayasu Hospital, Urayasu City, Japan. Fully informed written consent was obtained from all study participants.

Patients

Patients were treated with aflibercept for ME due to BRVO between June 2015 and April 2016. The inclusion criteria were as follows: age ≥ 18 years; symptomatic BRVO with retinal edema involving the foveal center; and foveal thicknesses >300 μm at the initial visit (measured by optical coherence tomography). Exclusion criteria included patients who had received intravitreal bevacizumab (IVB) injection, scatter photocoagulation, or grid laser photocoagulation for ME. The patients were classified into two groups, a treatment-naïve group subsequently treated with IVA and a switching group initially treated with intravitreal ranibizumab (IVR) injection and then switched to IVA because of the recurrence of ME.

Visual acuity and central macular thickness (CMT) were measured at preinjection and at 1 week and 1 month after the IVA. The ratio of patients in the treatment-naïve and switching groups in which the CMT was <300 μm at 1 month after the IVA was compared. The best-corrected visual acuity (BCVA) was measured by using a Landolt chart and converted to the logarithm of the minimum angle of resolution (logMAR).

Preinjection parameters in the switching group were correlated with a CMT <300 μm at 1 month after the IVA and a logMAR ≤ 0.15 (Snellen chart 20/28) at 1 month after the IVA. The preinjection parameters included age; sex; the duration from onset; the number of IVR injections before switching to IVA; and presence or absence of hypertension, diabetes, cystoid ME, subretinal fluid, and epiretinal membrane (ERM).

Statistical analysis

Data were analyzed by using StatView software for Windows (SAS, Cary, NC, USA). The repeated measures analysis of variance and Dunnett's test of multiple comparisons were used for comparisons at different time points before and after the injections, as a statistical test for related, not

independent groups, was required. Fisher's exact test was used to compare the ratios between the two groups. The Mann–Whitney *U* test was used to compare the age, the duration from onset, the number of IVR injections before the IVA injection, and CMT at preswitching. Fisher's exact test was used for categorical variables such as sex and the presence or absence of hypertension, diabetes, cystoid ME, subretinal fluid, and ERM. Multivariate logistic regression was used to analyze the preswitch parameters. $P < 0.05$ was accepted as statistically significant.

Results

Baseline characteristics

A total of 27 eyes from 27 patients comprised both the treatment-naïve and switching groups. The mean age was 66.4 ± 11.0 years in the treatment-naïve group and 72.0 ± 8.4 years in the switching group. The preinjection characteristics of the patients in both groups are summarized in Table 1.

Visual acuity and CMT

Changes in the BCVA and CMT from the treatment-naïve and switching groups are shown in Figures 1 and 2, respectively. In the treatment-naïve group, the BCVA improved from a logMAR value of 0.49 (20/62) at preinjection to 0.34 (20/44) at 1 week post-IVA and 0.27 (20/37) at 1 month post-IVA. Compared with the preinjection, there was a significant improvement in BCVA at both 1 week and 1 month post-IVA. In the switching group, the BCVA improved from a logMAR value of 0.48 (20/60) at preinjection to 0.44 (20/55) at 1 week post-IVA and 0.39 (20/49) at 1 month post-IVA. Compared with the preinjection, there was no significant improvement in BCVA at 1 week post-IVA, but there was a significant improvement in BCVA at 1 month post-IVA.

Table 1 Patient demographics and characteristics

| Contents | Treatment-naïve group | Switching group |
|-------------------------------|-----------------------|--------------------|
| Age, mean (SD), years | 66.4 (11.0) | 72.0 (8.4) |
| Sex, male/female | 11/16 | 10/17 |
| Number of IVR | – | 2.9 (2.0) |
| Visual acuity logMAR, Snellen | 0.49 (0.38), 20/60 | 0.48 (0.29), 20/60 |
| Hypertension, +/- | 11/16 | 14/13 |
| Diabetes, +/- | 4/23 | 4/23 |
| CMT, μm | 559.0 (161.9) | 511.6 (152.5) |
| CME, +/- | 17/10 | 17/10 |
| SRF, +/- | 10/17 | 5/22 |
| ERM, +/- | 1/26 | 5/22 |

Note: Both groups comprised 27 eyes of 27 patients.

Abbreviations: SD, standard deviation; IVR, intravitreal ranibizumab; logMAR, logarithm of the minimum angle of resolution; CMT, central macular thickness; CME, cystoid macula edema; SRF, subretinal fluid; ERM, epiretinal membrane.

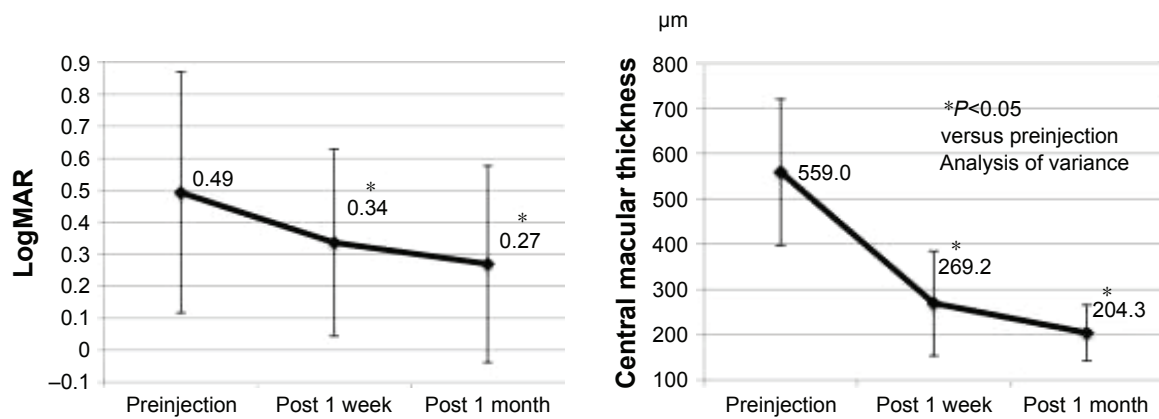


Figure 1 Improvement of BCVA and CMT from preinjection in the treatment-naïve group. There was a significant improvement at 1 week and 1 month post-IVA for both the BCVA and CMT.

Abbreviations: BCVA, best-corrected visual acuity; CMT, central macular thickness; IVA, intravitreal aflibercept.

In the treatment-naïve group, the mean CMT decreased from 559.0 μm at preinjection to 269.2 μm at 1 week post-IVA and 204.2 μm at 1 month post-IVA. In the switching group, the mean CMT decreased from 511.7 μm at preinjection to 265.2 μm at 1 week post-IVA and 238.2 μm at 1 month post-IVA. Compared with the preinjection, there was a significant decrease in the mean CMT at both 1 week and 1 month post-IVA in both the groups.

There were 26 of 27 eyes (96.3%) in the treatment-naïve group and 23 of 27 eyes (85.2%) in the switching group where the CMT was <300 μm at 1 month post-IVA, but there was no significant difference between the two groups ($P=0.35$).

Preswitch parameter associated with a beneficial response

In the switching group, univariate analysis showed that age and duration from onset were preswitch parameters associated with a decreased logMAR of ≤ 0.15 (20/28) at 1 month post-IVA (Table 2). Here, multivariate logistic regression

analysis showed that younger age was an independent preswitch parameter associated with a logMAR ≤ 0.15 (20/28). Univariate analysis also showed that the absence of ERM in the switching group was a preswitch parameter associated with a CMT <300 μm at 1 month post-IVA (Table 3).

Discussion

Numerous studies have reported on the use of anti-VEGF therapies to treat ME due to BRVO.^{3–11,27–29} The BRAVO and HORIZON studies were large-scale studies that evaluated the effectiveness of IVR treatment for ME due to BRVO,^{3,27} while VIBRANT study investigated the efficacy of IVA treatment.²⁸ There are numerous reports describing switch therapy for age-related macular degeneration (AMD),^{30–34} but few reports describe the use of switch therapy for RVO.^{24,25,35} Switching from steroid to anti-VEGF injections for RVO,³⁵ switching from IVR to IVA for CRVO,²⁴ and switching from IVB or IVR to IVA for CRVO have all been previously reported.²⁵ For ischemic CRVO, Lehmann-Clarke et al found

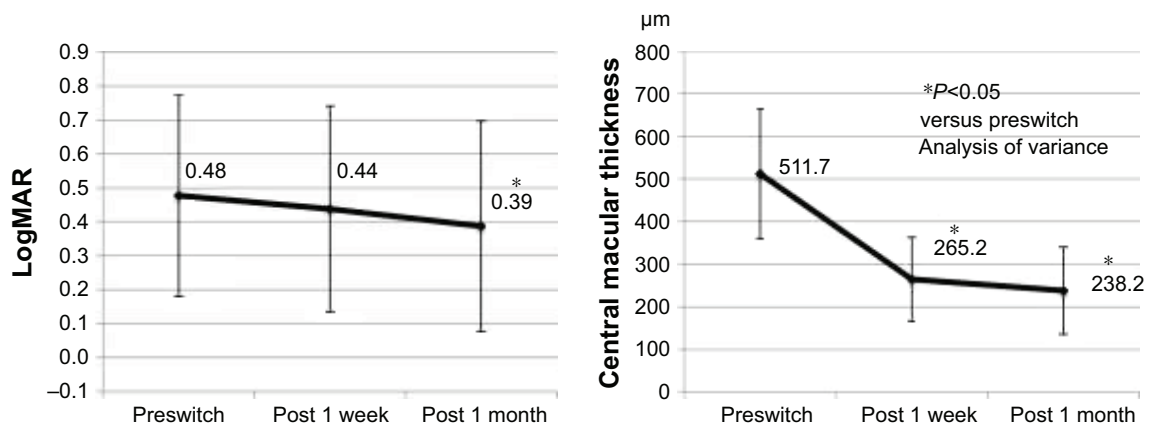


Figure 2 Improvement of BCVA and CMT from preswitch in the switching group. There was a significant improvement in BCVA at 1 month post-IVA and a significant improvement in CMT at 1 week and 1 month post-IVA.

Abbreviations: BCVA, best-corrected visual acuity; CMT, central macular thickness; IVA, intravitreal aflibercept.

Table 2 Preswitching factors associated with visual acuity at 1 month post-IVA

| Variable factors | Visual acuity (logMAR) | | | Logistic regression analysis | | |
|-----------------------|------------------------|---------------|---------|------------------------------|-------------|---------|
| | ≤0.15 | >0.15 | P-value | Crude odds ratio | 95% CI | P-value |
| Age, mean (SD), years | 66.0 (8.5) | 75.1 (6.7) | 0.015 | 1.201 | 1.027–1.403 | 0.02 |
| Sex, male/female | 5/4 | 5/13 | 0.16 | | | |
| Duration from onset | 16.4 (17.7) | 27.2 (19.9) | 0.035 | 1.047 | 0.983–1.115 | 0.15 |
| Number of IVR | 2.9 (2.8) | 2.9 (1.6) | 0.44 | | | |
| Hypertension, +/- | 4/5 | 10/8 | 0.44 | | | |
| Diabetes, +/- | 1/8 | 3/15 | 0.59 | | | |
| CMT, μm | 442.7 (120.7) | 546.2 (158.2) | 0.09 | | | |
| CME, +/- | 6/3 | 11/7 | 0.56 | | | |
| SRF, +/- | 0/9 | 5/13 | 0.11 | | | |
| ERM, +/- | 2/7 | 3/15 | 0.55 | | | |

Note: Younger age was associated with a good BCVA at 1 month postinjection in the switching group.

Abbreviations: logMAR, logarithm of the minimum angle of resolution; CI, confidence interval; SD, standard deviation; IVR, intravitreal ranibizumab; CMT, central macular thickness; CME, cystoid macular edema; SRF, subretinal fluid; ERM, epiretinal membrane; BCVA, best-corrected visual acuity.

that switching from IVR to IVA made the injection interval longer.²⁴ Therefore, this study would benefit from observing longer follow-up periods and consideration of the length of injection intervals.

No studies investigated switching from other anti-VEGF therapies to aflibercept, but switching from IVB to dexamethasone implants for treating ME due to BRVO has been reported.³⁵ By switching from IVB to dexamethasone or from dexamethasone to IVB, both visual acuity and CMT were significantly improved. In this study, switching to IVA from IVR showed both functional and anatomical improvement, as both the visual acuity and CMT significantly improved at 1 month postinjection.

At 1 month post-IVA, there was no significant difference between the treatment-naïve and switching groups for the CMT becoming $\leq 300 \mu\text{m}$. However, the background

characteristics of the two groups were different, so a simple comparison was not suitable. The difference in the durations from disease onset between the two groups was large, which can influence the short-term CMT.

In addition, this study showed that the visual acuity of a younger patient increased to a logMAR of ≤ 0.15 (20/28) at 1 month when switching to post-IVA. It is thought that older patients did not adequately recover their retinal function when the ME disappears. Furthermore, Yasuda et al reported that age is one of the risk factors associated with the onset of RVO,³⁶ so age is also thought to be related to the severity of RVO.

In the switching group, the CMT was rarely $< 300 \mu\text{m}$ at 1 month post-IVA in ME patients with ERM. A previous study reported a case of AMD with vitreomacular adhesion that was insensitive to anti-VEGF treatment.³⁷ This report involved a very short timeframe, but it had similar outcomes for BRVO as the present report. It is thought that pro re nata dosing involving IVA is sufficient for switching patients without ERM because of their sensitivity to IVA, but switching of patients with ERM would likely require multiple injections. However, this study only examined patients until 1 month post-IVA and did not examine whether the ME improved after the second IVA, so in these patients it is necessary to follow the progress of the ME after multiple IVA injections. In addition, in patients with ME due to BRVO with ERM, it might be necessary to perform a vitrectomy.

Limitations

The limitations of this study included the small sample size and the short-term follow-up period of 1 month after switching. To overcome these concerns, future studies should determine the effects of IVA over a longer timeframe.

Table 3 Preswitching parameters associated with CMT at 1 month post-IVA

| CMT at 1 month post-IVA | <300 μm | $\geq 300 \mu\text{m}$ | P-value |
|-------------------------|--------------------|------------------------|---------|
| Age, mean (SD), years | 71.4 (8.9) | 75.5 (3.7) | 0.34 |
| Sex, male/female | 9/14 | 1/3 | 0.52 |
| Duration from onset | 20.7 (17.9) | 40.3 (23.0) | 0.07 |
| Number of IVR | 2.8 (2.9) | 3.3 (2.1) | 0.62 |
| Hypertension, +/- | 12/11 | 2/2 | 0.67 |
| Diabetes, +/- | 3/20 | 1/3 | 0.50 |
| CMT, μm | 498.8 (493.6) | 585.8 (177.6) | 0.31 |
| CME, +/- | 3/20 | 2/2 | 0.48 |
| SRF, +/- | 4/19 | 1/3 | 0.58 |
| ERM, +/- | 2/21 | 3/1 | 0.01 |

Note: Absence of the epiretinal membrane was associated with improvement of the CMT at 1 month postinjection in the switching group.

Abbreviations: IVA, intravitreal aflibercept; SD, standard deviation; IVR, intravitreal ranibizumab; CMT, central macular thickness; CME, cystoid macular edema; SRF, subretinal fluid; ERM, epiretinal membrane.

Conclusion

The treatment outcomes at 1 month post-IVA injection for patients with ME due to BRVO were reported. IVA is temporarily effective for treating ME due to BRVO regardless of a history of IVR use.

Disclosure

The authors report no conflicts of interest in this work.

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