Outcome of Switching Anti-VEGF Agents at Fixed Intervals to Treat Eyes With Macular Edema Secondary to Branch Retinal Vein Occlusion

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Research note

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Abstract

Objective

To determine whether switching intravitreal injections of ranibizumab or aflibercept to the other will affect the interval of subsequent injections in patients with macular edema secondary to branch retinal vein occlusion (BRVO).

Results

The medical charts of 16 eyes of 16 patients were reviewed. After injections of ranibizumab or aflibercept for >3 times/year, the type of anti-vascular endothelial growth factor agent was switched. A comparison was made of the average injection interval for the one year before switching and the interval of the first two injections post-switching. In the group that switched from ranibizumab to aflibercept (R to A group, n=8), the interval before was 85.4 ± 6.6 days which was significantly increased to 125.9 ± 23.2 days post-switching ($P=0.0013$). In the A to R group (n=8), a significant shortening from 103.9 ± 11.8 days before to 85.9 ± 12.6 days was observed ($P=0.007$). In the R to A group, the central retinal thickness at a recurrence was 522.1 ± 79.6 μm which decreased significantly to 419.3 ± 64.5 μm post-switching ($P=0.005$). The results suggest that the intervals can be different between ranibizumab and aflibercept in patients with macular edema secondary to BRVO who required repeat injections.

Introduction

The major cause of the decrease of visual function in eyes with a branch retinal vein occlusion (BRVO) is macular edema. The retinal ischemia caused by the blockage induces an increase in the levels of intraocular vascular endothelial growth factor (VEGF) which then enhances the vascular permeability of the blood vessels. This then results in a leakage and macular edema.^[1]

Anti-VEGF agents have been shown to be an effective treatment for the BRVO-induced macular edema.^[2, 3] At present, two anti-VEGF agents, ranibizumab and aflibercept, are widely used to treat patients with a BRVO. The use of aflibercept for central retinal vein occlusion (CRVO) with macular edema requires fewer injections than ranibizumab suggesting that the duration of its effectiveness may differ from that of ranibizumab.^[4] However, a direct comparison of the duration of effectiveness has not been determined for these two agents for BRVO. Relevant to our study, two earlier studies found that the interval of injections was prolonged when ranibizumab was switched to aflibercept in patients with macular edema secondary to BRVO.^[5, 6] However, the prolongation of injection interval after switching agents may be influenced by the time-dependent attenuation of the natural progression of the disease process.^[7, 8] For this reason, it is important to examine cases in which patients have been switched from aflibercept to ranibizumab.

Thus, the purpose of this study was to compare the interval of anti-VEGF injections after ranibizumab was switched to aflibercept or when aflibercept was switched to ranibizumab in patients with macular

edema secondary to BRVO. To accomplish this, we reviewed the medical records of patients who had undergone a switching of ranibizumab to aflibercept (R to A) or from aflibercept to ranibizumab (A to R) on the interval of the injections, and the degree of macular edema.

Methods

Sixteen eyes of 16 patients with macular edema associated with a BRVO were studied. At least 3 intravitreal injections of an anti-VEGF agent, ranibizumab (Lucentis®; Novartis Pharma, Basel, Switzerland) or aflibercept (Eylea®; Bayer Pharma AG, Berlin, Germany) were given for one year, the pre-switch period, between July 2015 and December 2018. The patients were then switched to the other type of anti-VEGF agent. The reason for switching agents was because the patient who had an aversion to get repeated same injections accepted our suggestion to change to another type of agent.

The general protocol of our hospital encourages patients to visit their doctor every month at which time optical coherence tomography (OCT; 3D OCT-2000, Topcon) and visual acuity measurements were performed. The OCT images were used to measure the central retinal thickness (CRT), and if the CRT was $\geq 350 \mu\text{m}$, a recurrence of the macular edema was considered to have occurred. Then, an anti-VEGF intravitreal injection was given with the pro re nata (PRN) treatment protocol. Patients who had undergone other ocular treatments such as topical steroids, intraocular surgery, and scatter and grid laser photocoagulation at the pre-switch period were excluded.

Retrospective investigations of the medical records of the patients were performed. A comparison between an average injection interval for the pre-switch period and the interval of the first two injections after switching the anti-VEGF agents was considered the primary endpoint. Comparisons of the CRT before and after switching agents were considered at the time of a recurrence and at the time one month after the injection.

Statistical analyses

The significance of the differences in the pre-injection demographic data of the R to A and the A to R groups was determined by Mann-Whitney U tests or Fisher’s exact tests. The significance of the changes in the injection intervals and CRT before and after switching agents was made using paired *t*-tests. A *P*-value < 0.05 was taken to be statistically significant.

Results

The patients were divided into two groups: the R to A group (4 men and 4 women) and the A to R group (5 men and 3 women). The demographics of the patients in the two groups are summarized in Table 1. There were no significant differences in the mean age, male-female ratio, best-corrected visual acuity, CRT, estimated duration from onset, frequency of anti-VEGF injections in the pre-switch period, and previous photocoagulations between the two groups.

Table 1. Demographics of patients

	ranibizumab to aflibercept (n=8)	aflibercept to ranibizumab (n=8)	p value
Age in years	69.9 ± 7.2	68.8 ± 7.6	0.764 ^a
Sex, Male/Female	4/4	5/3	0.61 ^b
BCVA at baseline (log-MAR)	0.25 ± 0.21	0.34 ± 0.28	0.751 ^a
CRT at baseline	647.1 ± 98.8	617.0 ± 74.5	0.713 ^a
Duration of symptoms before switch (months)	33.0 ± 9.2	26.8 ± 7.8	0.346 ^a
Number of injections before switch (times / year)	3.50 ± 0.75	3.25 ± 0.46	0.438 ^a
Previous photocoagulation for capillary non-perfusion	5	6	0.59 ^b

Values are the means ± standard deviations.

n, number of eyes; BCVA, best-corrected visual acuity; log-MAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness.

^aMann-Whitney U test, ^bFisher's exact test.

In the R to A group, the mean injection interval before switching was 85.4 ± 6.6 days which was significantly increased to 125.9 ± 23.2 days after the switch ($P = 0.0013$; Fig. 1a). In the A to R group, there was a significant shortening of injection interval from 103.9 ± 11.8 days before to 85.9 ± 12.6 days after switching agents ($P = 0.007$; Fig. 1b). In the R to A group, the percentage increase in the injection interval before and after switching agents was $\pm 10\%$ in 1 eye (12.5%), 10–30% in 1 eye (12.5%), and $\geq 30\%$ in 6 eyes (75%). In the A to R group, the percentage shortening of the intervals before and after switching agents was $\pm 10\%$ in 2 eyes (25%), 10–30% in 5 eyes (62.5%), and $\geq 30\%$ shortening in 1 eye (12.5%; Fig. 1c).

The mean CRTs at one month after the anti-VEGF injections was 228.7 ± 31.8 μm before and 230.4 ± 45.2 μm after the switch in the R to A group ($P > 0.05$; Fig. 2a) and 263.4 ± 28.0 μm before and 274.5 ± 30.4 μm after the switch in the A to R group ($P > 0.05$; Fig. 2c). The mean CRTs at a recurrence in the R to A group, was 522.1 ± 79.6 μm before and 419.3 ± 64.5 μm after the switch, and there was a significant difference in the degree of macular edema ($P = 0.005$; Fig. 2b). In contrast, the CRTs was 433.8 ± 79.6 μm and 472.5 ± 75.3 μm at a recurrence in the A to R group, and these findings showed that the differences in the degree of macular edema was not significantly changed ($P > 0.05$; Fig. 2d).

Discussion

We observed a prolongation of the injection interval after switching to aflibercept and shortening of injection interval after switching to ranibizumab. These findings suggest that the prolongation and shortening of the injection interval were related to a difference in the duration of effectiveness of the two agents.

In the R to A group, average injection interval before the switch was 85 days, and it increased significantly to 126 days after the switch. The increase in the injection intervals was 41 days which is 1.48 times longer than the average injection interval during the pre-switch period. In a prospective study, Casselholm et al^[4] compared the injection intervals for ranibizumab and aflibercept in eyes with a CRVO performed

with the treat-and-extend protocol. They reported that the average injection interval for ranibizumab was 6.6 week and that for aflibercept was 10.0 weeks. These findings indicated that the effects of aflibercept lasted 1.5X longer than ranibizumab. Thus, their findings are comparable to our percentage prolongation of the injection interval in the R to A group.

There have been many studies on the effectiveness of switching from ranibizumab to aflibercept in patients with macular edema secondary to a BRVO. The patients studied can be classified into two types; one type is the patient who was not responding to ranibizumab and were then switched to aflibercept,^[5,9,10] and the other type was the patient who had a difference in the duration of the effectiveness between two agents as indicated by the lengthening of the interval after switching to aflibercept.^[6] The difficulty in comparing these results is that there is a spontaneous healing in more than 30% of cases if macular edema secondary to BRVO develops within one year after the onset of BRVO.^[11] The RELATE study examined patients who had received ranibizumab treatment with a loading phase of 6 PRN injections for 3 years, and they found that the number of injections required for successful treatment decreased with time; 9.7 times in the first year, 6.9 times in the second year, and 4.0 times in the third year.^[12] Thus, we cannot eliminate the possibility that the prolongation of injection interval after switching to aflibercept was related to a natural attenuation of the disease progression. Therefore, after switching to ranibizumab, a prolongation of injection interval could also be expected. However, to our knowledge, there have been no studies performed to evaluate the change in the injection interval after switching therapy from aflibercept to ranibizumab in patients with BRVO. In our cases, in the A to R group, average injection interval before the switch was 104 days and after the switch to ranibizumab was 86 days. Therefore, the difference between the two injection intervals is 18 days, that is, 1.21 times shorter than the average injection interval after switching to ranibizumab. The results showed no prolongation of injection interval due to a time-dependent attenuation of the natural progression of the disease process.

The reason for the longer effectiveness of aflibercept is because it has different biochemical characteristics from ranibizumab. For example, aflibercept can bind not only to VEGF-A but also to other VEGF family members, such as VEGF-B and placental growth factor (PlGF). In addition, aflibercept has a strong affinity for VEGF-A.^[13] The intraocular PlGF levels are elevated in patients with macular edema secondary to BRVO suggesting that it may be involved in the recurrence of macular edema.^[14] In animal experiments, Stewart et al. reported that aflibercept had longer binding activity than ranibizumab.^[15] In addition, Niwa et al. compared the intraocular kinetics of ranibizumab and aflibercept after intravitreal injections in monkeys.^[16] They reported that the half-life of both agents in the aqueous after intravitreal injections was not significantly different, but aflibercept suppressed the VEGF level for a longer time. From these results, we can conclude that aflibercept has a longer period of effectiveness. This was true even after the agents decreased below the detection level which suggested that aflibercept has a better potential of preventing the recurrence of macular edema. Saishin et al. examined the effects of intravitreal injections of ranibizumab and aflibercept bimonthly on CRVO patients, and they reported that the CRT measured at the time of recurrence was thicker in the ranibizumab than the aflibercept group.^[17]

Their findings are consistent with the results of our study in showing the difference in the CRTs at the time of recurrence in the R to A group.

In conclusion, the injection interval can be different between ranibizumab and aflibercept in patients with macular edema secondary to BRVO. Because the difference of injection interval affects patient's medical cost, economic, or psychological burden, it is necessary to focus on the selection of agents for BRVO treatment as well as relieving the effects of macular edema by the anti-VEGF agents.

Limitations

Our study was limited due to its retrospective nature and small sample size. Another limitation is the different assessment period among pre-switching and after switching agents. On one hand, a one-year assessment period was set before switching agents, but the assessment period after switching agents was not the same as the one before switching agents. This is because patients have a tendency to ask physicians to switch back to the previous one when a shortening of the injection interval occurs due to switching agents. This indicates that the prolongation or shortening of the injection interval becomes a sufficient reason for patients to select the agent.

Abbreviations

BRVO: branch retinal vein occlusion; CRT: central retinal thickness; CRVO: central retinal vein occlusion; OCT: optical coherence tomography; PIGF: Placental growth factor; PRN: pro re nata; VEGF: vascular endothelial growth factor.

Declarations

Authors' contributions

TM collected the data, drafted the manuscript, made figures, and sought data analysis consultations. TK and AS conceptualized the study design, modified manuscript and data analyses. All authors read and approved the final manuscript.

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Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study complied with the tenets of the Declaration of Helsinki. This study was approved by Institutional Review Board/Ethics Committee of University of Ehime Graduate School of Medicine Hospital (approval No.: 1903012). Written informed consent was obtained from the patient to publish and report individual patient data.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to the present study.

Consent for publication

Not applicable.

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Figures

Figure 1

Figure 1

Injection intervals before and after switching anti-vascular endothelial growth factors (anti-VEGFs). a: Group that switched from ranibizumab to aflibercept (R to A). P-value, paired t test. b: Group that switched aflibercept to ranibizumab (A to R). P-value, paired t test. c: Percentage change of injection interval before and after switching anti-VEGF agents.

Figure 2

Figure 2

Central retinal thickness (CRT) before and after switching anti-VEGF agents. a: In the R to A group, the CRT before and after switching agents at one month after the anti-VEGF injection. b: In the R to A group, the CRT before and after switching agents at a recurrence. c: In the A to R group, the CRT before and after switching agents at one month after the anti-VEGF injection. d: In the A to R group, the CRT before and after switching agents at a recurrence. P-value, paired t test.