



Article

# Macular Sensitivity after Intravitreal Ranibizumab Injection for Macular Edema in Central Retinal Vein Occlusion: One versus Three Initial Monthly Injections

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**Abstract:** Background: We aimed to compare the macular sensitivity after one initial intravitreal injection of an anti-vascular endothelial growth factor (VEGF) agent followed by pro re nata (PRN) dosing with that after three initial monthly injections followed by PRN dosing in patients with central retinal vein occlusion (CRVO) and macular edema. Methods: We included 20 eyes of 20 patients with treatment-naïve macular edema in CRVO and followed them for 12 months after intravitreal ranibizumab injection (IRI). Before and 1, 3, 6, and 12 months after IRI, macular sensitivity within the central 1 mm, 3 mm, and 6 mm fields was measured with an MP3 microperimeter and best-corrected visual acuity (BCVA) was assessed. Eleven eyes received one initial IRI (1 + PRN group), and nine received three initial monthly IRIs (3 + PRN group). PRN injections were performed when fovea exudative changes were evident. Results: Mean macular sensitivity within the central 1 mm, 3 mm, and 6 mm fields significantly improved from baseline to month 12 in all treated eyes. We found no significant differences in macular sensitivity in the central 1 mm, 3 mm, or 6 mm fields between the two groups at month 1, 3, 6, or 12. The choice of treatment regimen (1 + PRN or 3 + PRN) showed no association with either macular sensitivity in the central 1 mm, 3 mm, and 6 mm fields or BCVA at month 12. Conclusions: These findings suggest that a 1 + PRN regimen improves macular sensitivity to a similar extent as a 3 + PRN regimen.

**Keywords:** central retinal vein occlusion; macular edema; ranibizumab; macular sensitivity; regimen



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## 1. Introduction

In patients with central retinal vein occlusion (CRVO), visual impairment is most often caused by macular edema [1,2]. The vascular occlusion associated with macular edema was found to increase levels of vascular endothelial growth factor (VEGF) [3], and this finding led to the development of intravitreal anti-VEGF therapy. The rationale for anti-VEGF therapy is that decreasing the levels of VEGF decreases macular edema and consequently improves visual function [4]. Several randomized studies showed that visual prognosis was better if intravitreal anti-VEGF injections were repeated [5–8]. For example, a phase 3 study on the efficacy and safety of ranibizumab for the treatment of macular edema after CRVO (CRUISE) [5] showed rapid and sustained visual improvement in patients who received six monthly injections in the first 6 months followed by pro re nata (PRN) injections in the subsequent 6 months.

However, the reason why so many injections of an intravitreal anti-VEGF agent are required to obtain a certain level of improvement in macular edema after CRVO is not well understood. Furthermore, although administering multiple injections of such agents has favorable treatment outcomes, it may increase the risk of systemic or ocular complications and can place mental, physical, and economic burdens on patients [5,9,10]. Recently,

regimens of one or three initial injections followed by PRN injections (1 + PRN and 3 + PRN, respectively) were reported to achieve similar 12-month visual outcomes in anti-VEGF therapy for macular edema with CRVO [11].

Visual function is not limited to visual acuity and includes also sensitivity to contrast; perception of colors, depth, and motion; and the ability to perform functional tasks such as driving and walking down stairs [12]. Thus, it is associated also with fovea function. Therefore, macular sensitivity may be important also in CRVO because CRVO affects the entire macula region. This hypothesis is supported by findings that macular sensitivity provides a better assessment of visual function in CRVO than visual acuity does [13,14].

Because the 1 + PRN regimen was found to be effective in improving visual acuity, we hypothesized that it may also show efficacy in improving macular sensitivity. Therefore, in this study we treated patients with macular edema secondary to CRVO with one or three monthly initial intravitreal ranibizumab injections (IRIs) followed by PRN. We measured macular sensitivity with an MP-3 microperimeter (MP), an instrument that combines digital fundus imaging with automated perimetry and has been used to assess macular sensitivity after anti-VEGF therapy in CRVO [15,16], and compared the changes between the two regimens.

## 2. Materials and Methods

### 2.1. Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki. After approval by the Review Committee of the Institutional Research Board of Tokyo Medical University Hachioji Medical Hospital (IRB No. H-132), 20 CRVO patients with macular edema were enrolled between June, 2018 and June, 2020 in the study and underwent IRI at Tokyo Medical University Hachioji Medical Hospital. After obtaining informed consent from the patients, an IRI was performed via the pars plana using a 30-gauge needle. Injections were performed at 3.5 mm posterior to the limbus.

The study was performed in treatment-naïve patients with visual impairment due to macular edema associated with non-ischemic CRVO. CRVO was diagnosed by fundus examination and spectral-domain optical coherence tomography (SD-OCT). Inclusion criteria were as follows: symptoms associated with macular edema in CRVO; involvement of the center of the fovea; foveal thickness greater than 300  $\mu\text{m}$  as measured by OCT at the initial study visit; at least 30 years old; onset of symptoms less than 6 months before the initial examination; and best-corrected visual acuity (BCVA) between 0.1 and 1.3 log-arithms of the minimum angle of resolution (logMAR). Exclusion criteria were ischemic CRVO, defined as capillary non-perfusion in ten or more disc areas [17], other chorioretinal disease (e.g., diabetic retinopathy, hypertension retinopathy, retinal macroaneurysm, age-related macular degeneration, myopic choroidal neovascularization, uveitis, and retinitis pigmentosa); impending CRVO; senile cataract that resulted in poor image quality; coexisting ocular disease (i.e., epiretinal membrane or glaucoma); systemic disorders other than hypertension or hypercholesterolemia; and history of intravitreal anti-VEGF injection, intraocular administration of corticosteroids, retinal photocoagulation, or pars plana vitrectomy. Fluorescein angiography was performed at the initial visit to determine the area of capillary non-perfusion.

### 2.2. Treatment for Macular Edema Associated with Central Retinal Vein Occlusion

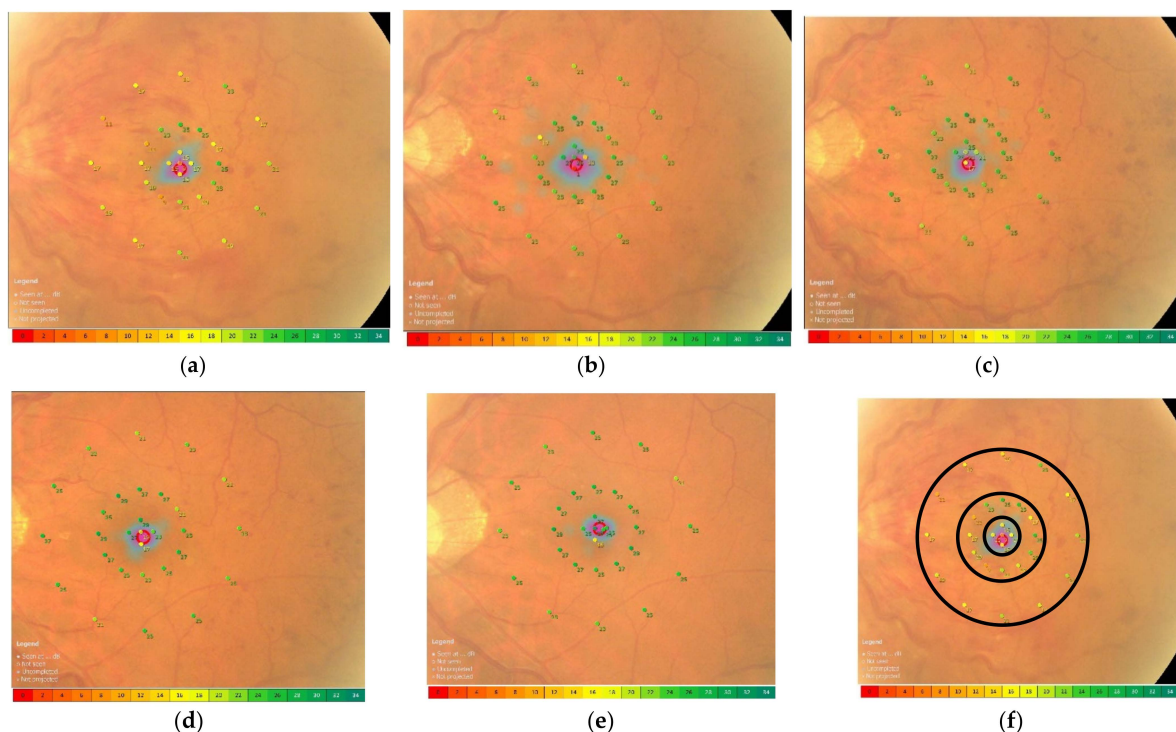
Consecutive patients were assigned to receive 1 initial IRI ( $n = 11$ ; Lucentis; 0.5 mg in 0.05 mL; Genentech, Inc., South San Francisco, CA, USA) or 3 initial monthly IRIs ( $n = 9$ ). Subsequently, monthly eye examinations were performed every month for 12 months, and PRN injections were administered when OCT showed macular edema or serous retinal detachment at the fovea. IRI was the only treatment administered for macular edema. IRI was administered with the aim to decrease levels of VEGF and, consequently, decrease macular edema and improve visual function [4].

### 2.3. Clinical Parameters

All patients underwent a full ophthalmologic and ocular examination at baseline before IRI and then at monthly intervals. At baseline, the Landolt chart was used to assess BCVA as a decimal value, which was then converted to the logMAR value, and at follow-up, BCVA was assessed with the logMAR chart (5 m; NEITZ LVC-10, Tokyo, Japan). Central macular thickness (CMT) was calculated with Spectralis software on the basis of mapping images obtained by Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). We assessed CMT in 2 ways: (1) as the macular thickness in the central 1 mm field calculated by the Spectralis software from the mapping image and (2) as the distance between the inner limiting membrane and retinal pigment epithelium (including serous retinal detachment, if present) calculated by computer software.

### 2.4. Functional Mapping by Microperimetry

Microperimetry with the MP-3 instrument (Nidek, Gamagori, Japan) was performed at baseline and 1, 3, 6, and 12 months after IRI (Figure 1a–e). MP-3 requires a pupil diameter of greater than 4 mm, which was the case in all patients. It was performed with the 4–2 full threshold staircase strategy and a background luminance of 31.4 apostilb (Goldmann size III stimulus). The MP-3 has a maximum luminance of 10,000 apostilb, resulting in a dynamic stimulus range of 0 to 34 dB. The size of the fixation target was adjusted depending on each patient's visual acuity. An advantage of the MP-3 is that it automatically adjusts for any refractive error in an eye [18]. The MP-3 generated macular sensitivity maps for the central 20 degrees of the macula. Macular sensitivity at 5 different stimulus locations was used to calculate the mean sensitivity in the central 1 mm field; at 17 different stimulus locations, to calculate the mean sensitivity in the central 3 mm field; and at 29 different stimulus locations, to calculate the mean sensitivity in the central 6 mm field (Figure 1f).



**Figure 1.** Measurement of macular sensitivity by microperimetry. The figures show a typical macular sensitivity map obtained with the MP-3 system. MP-3 maps at (a) baseline; (b) 1 month after intravitreal ranibizumab injection (IRI); (c) 3 months after IRI; (d) 6 months after IRI; and (e) 12 months after IRI. (f) Mean macular sensitivity was calculated in the central 1 mm, 3 mm, and 6 mm fields. The MP-3 system tested the foveal region (central 1 mm field) at 5 points and the macular regions (central 3 mm and 6 mm fields) at 17 and 29 points, respectively.

### 2.5. Statistical Analysis

All analyses were performed with SAS System 9.4 software (SAS Institute Inc., Cary, NC, USA). Results are presented as the mean  $\pm$  SD or as the frequency. Comparisons between the two different regimen groups were performed with an unpaired *t*-test, and bivariate relationships were assessed with Pearson's correlation coefficient. The impact of individual factors was analyzed by a stepwise multiple linear regression model. Two-tailed *p* values of less than 0.05 were considered to indicate statistical significance.

### 3. Results

A total of 28 eyes were excluded, as follows: ischemic CRVO, five eyes; other chorioretinal disease, five eyes; impending CRVO, three eyes; senile cataract that resulted in poor image quality, two eyes; coexisting ocular disease, two eyes; systemic disorders other than hypertension or hypercholesterolemia, two eyes; history of intravitreal anti-VEGF injection, four eyes; history of intraocular administration of corticosteroids, two eyes; history of retinal photocoagulation, two eyes; and history of pars plana vitrectomy, one eye. We administered IRI to 20 eyes in 20 patients with macular edema associated with CRVO. Table 1 shows the patient demographic and baseline ocular characteristics. A mean of  $4.2 \pm 2.2$  injections were administered in the 12-month follow-up. In the whole group, mean logMAR BCVA improved significantly from  $0.44 \pm 0.30$  ( $62.7 \pm 15.2$  ETDRS letters) at baseline to  $0.07 \pm 0.19$  ( $80.7 \pm 12.3$  ETDRS letters) at month 12 ( $p < 0.001$ ); mean CMT decreased significantly from  $701 \pm 168$   $\mu$ m at baseline to  $264 \pm 78$   $\mu$ m at month 12 ( $p < 0.001$ ); mean macular sensitivity within the central 1 mm field improved significantly from  $14.2 \pm 5.72$  at baseline to  $22.3 \pm 6.32$  at month 12 ( $p < 0.001$ ); mean macular sensitivity within the central 3 mm field improved significantly from  $17.3 \pm 5.15$  at baseline to  $23.5 \pm 5.64$  at month 12 ( $p < 0.001$ ); and mean macular sensitivity within the central 6 mm field improved significantly from  $18.7 \pm 4.91$  at baseline to  $23.3 \pm 5.18$  at month 12 ( $p < 0.001$ ).

**Table 1.** Baseline and final clinical characteristics of eligible patients with macular edema in central retinal vein occlusion.

| Findings                         | Total                                   | 1 + PRN Group ( <i>n</i> = 11)          | 3 + PRN Group ( <i>n</i> = 9)           | <i>p</i> Value |
|----------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|----------------|
| <b>Baseline</b>                  |                                         |                                         |                                         |                |
| Age (years)                      | $62.2 \pm 11.5^\ddagger$                | $59.0 \pm 13.5^\ddagger$                | $66.1 \pm 7.38^\ddagger$                | 0.176          |
| Gender (female/male)             | 9/11                                    | 3/8                                     | 6/3                                     | 0.078          |
| Duration of macular edema (days) | $30.8 \pm 23.9^\ddagger$                | $36.3 \pm 24.6^\ddagger$                | $24.1 \pm 22.5^\ddagger$                | 0.269          |
| Hypertension                     | 15                                      | 8                                       | 7                                       | 0.795          |
| Systolic blood pressure (mmHg)   | $139 \pm 19^\ddagger$                   | $140 \pm 12^\ddagger$                   | $137 \pm 26^\ddagger$                   | 0.723          |
| Diastolic blood pressure (mmHg)  | $87 \pm 12^\ddagger$                    | $88 \pm 12^\ddagger$                    | $86 \pm 13^\ddagger$                    | 0.667          |
| Hyperlipidemia                   | 9                                       | 5                                       | 4                                       | 0.964          |
| BCVA (logMAR, ETDRS letters)     | $0.44 \pm 0.30, 62.7 \pm 15.2^\ddagger$ | $0.44 \pm 0.33, 62.6 \pm 16.4^\ddagger$ | $0.44 \pm 0.29, 62.7 \pm 14.4^\ddagger$ | 0.966          |
| CMT ( $\mu$ m)                   | $701 \pm 168^\ddagger$                  | $718 \pm 182^\ddagger$                  | $679 \pm 157^\ddagger$                  | 0.610          |
| MS within 1 mm (dB)              | $14.2 \pm 5.72^\ddagger$                | $13.3 \pm 5.68^\ddagger$                | $15.4 \pm 5.88^\ddagger$                | 0.427          |
| MS within 3 mm (dB)              | $17.3 \pm 5.15^\ddagger$                | $17.1 \pm 4.88^\ddagger$                | $17.6 \pm 5.75^\ddagger$                | 0.847          |
| MS within 6 mm (dB)              | $18.7 \pm 4.91^\ddagger$                | $18.6 \pm 4.33^\ddagger$                | $18.7 \pm 5.80^\ddagger$                | 0.959          |

Table 1. Cont.

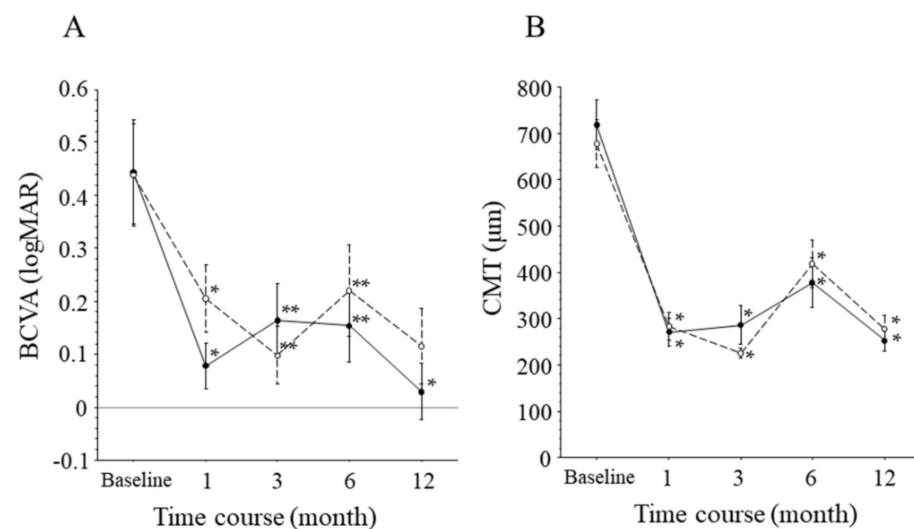
| Findings                                 | Total                      | 1 + PRN Group (n = 11)    | 3 + PRN Group (n = 9)      | p Value |
|------------------------------------------|----------------------------|---------------------------|----------------------------|---------|
| <i>Final</i>                             |                            |                           |                            |         |
| BCVA (logMAR)                            | 0.07 ± 0.19, 80.7 ± 12.3 ‡ | 0.03 ± 0.18, 83.8 ± 9.3 ‡ | 0.11 ± 0.21, 77.0 ± 14.9 ‡ | 0.341   |
| CMT (µm)                                 | 264 ± 78 ‡                 | 252 ± 71 ‡                | 278 ± 87 ‡                 | 0.465   |
| MS within 1 mm (dB)                      | 22.3 ± 6.32 ‡              | 23.4 ± 3.75 ‡             | 20.9 ± 8.57 ‡              | 0.399   |
| MS within 3 mm (dB)                      | 23.5 ± 5.64 ‡              | 24.9 ± 3.01 ‡             | 21.6 ± 7.57 ‡              | 0.193   |
| MS within 6 mm (dB)                      | 23.3 ± 5.18 ‡              | 24.8 ± 2.74 ‡             | 21.5 ± 6.91 ‡              | 0.168   |
| Number of intravitreal injections        | 4.2 ± 2.2 ‡                | 3.3 ± 2.3 ‡               | 5.2 ± 1.7 ‡                | 0.049   |
| Eyes that did not require PRN injections | 6                          | 4                         | 2                          | 0.492   |

BCVA = best-corrected visual acuity; CMT = central macular thickness; CRVO = central retinal vein occlusion; log MAR = logarithm of the minimum angle of resolution; MS = macular sensitivity; PRN = pro re nata; ‡ Mean ± standard deviation (SD).

Patient demographics and baseline ocular characteristics were similar between treatment groups (Table 1). Of the 20 eyes included, 11 (55.0%) received one initial IRI (1 + PRN group), and the remaining 9 (45.0%) received three initial monthly IRIs (3 + PRN group). The mean age of the 3 + PRN group was approximately 7 years higher than that of the 1 + PRN group, but the difference was not statistically significant. The mean number of IRIs was significantly lower in the 1 + PRN group than in the 3 + PRN group ( $3.3 \pm 2.3$  vs.  $5.2 \pm 1.7$ , respectively;  $p = 0.049$ , Table 1). Six (30.0%) of the 20 eyes did not require PRN IRI; this was the case in fewer patients in the 3 + PRN group (2/9: 22.2%) than in the 1 + PRN group (4/11: 36.4%), but the difference was not significant ( $p = 0.492$ , Table 1).

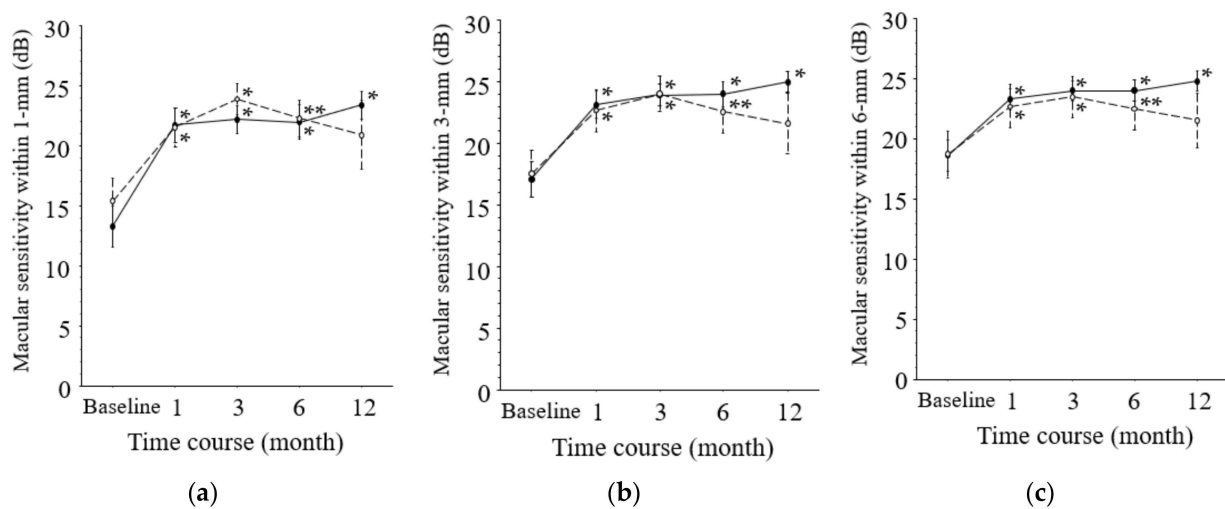
Both groups showed an improvement in BCVA and a subsequent rapid reduction in CMT. Mean BCVA improved significantly from baseline ( $0.44 \pm 0.33$ ) to months 1 ( $0.08 \pm 0.14$ ,  $p = 0.001$ ), 3 ( $0.16 \pm 0.23$ ,  $p = 0.047$ ), 6 ( $0.15 \pm 0.22$ ,  $p = 0.032$ ), and 12 ( $0.03 \pm 0.18$ ,  $p = 0.007$ ) in the 1 + PRN group and from baseline ( $0.44 \pm 0.29$ ) to months 1 ( $0.21 \pm 0.19$ ,  $p = 0.007$ ), 3 ( $0.09 \pm 0.16$ ,  $p = 0.010$ ), and 12 ( $0.11 \pm 0.21$ ,  $p = 0.034$ ) in the 3 + PRN group, but not from baseline to month 6 ( $0.22 \pm 0.26$ ,  $p = 0.137$ ) in the 3 + PRN group. No significant intergroup difference in BCVA was found at month 1 ( $p = 0.103$ ), 3 ( $p = 0.476$ ), 6 ( $p = 0.543$ ), or 12 ( $p = 0.341$ ; Figure 2A). Mean CMT improved significantly from baseline ( $719 \pm 182$  µm) to months 1 ( $271 \pm 103$  µm,  $p < 0.001$ ), 3 ( $286 \pm 141$  µm,  $p < 0.001$ ), 6 ( $377 \pm 179$  µm,  $p = 0.001$ ), and 12 ( $252 \pm 71$  µm,  $p < 0.001$ ) in the 1 + PRN group and also from baseline ( $679 \pm 157$  µm) to months 1 ( $283 \pm 90$  µm,  $p < 0.001$ ), 3 ( $226 \pm 29$  µm,  $p < 0.001$ ), 6 ( $419 \pm 155$  µm,  $p = 0.004$ ), and 12 ( $278 \pm 86$  µm,  $p < 0.001$ ) in the 3 + PRN group. No significant intergroup difference in CMT was found at month 1, 3, 6, or 12 ( $p = 0.788$ ,  $p = 0.223$ ,  $p = 0.592$ , and  $p = 0.465$ , respectively; Figure 2B).





**Figure 2.** Changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) in groups receiving 1 or 3 initial intravitreal injections of an anti-vascular endothelial growth factor followed by pro re nata dosing (1 + PRN and 3 + PRN, respectively). Both groups showed a rapid reduction in BCVA and CMT. (A) BCVA in the 1 + PRN group (solid line) vs. the 3 + PRN group (dashed line). (B) CMT in the 1 + PRN group (solid line) vs. the 3 + PRN group (dashed line). BCVA and CMT were not significantly different between the 2 groups at any of the study visits. \*  $p < 0.01$  vs. baseline, \*\*  $p < 0.05$  vs. baseline.

Mean macular sensitivity in the central 1 mm field significantly improved from baseline ( $13.3 \pm 5.68$  dB) to months 1 ( $21.7 \pm 4.65$  dB,  $p < 0.001$ ), 3 ( $22.2 \pm 3.83$  dB,  $p = 0.002$ ), 6 ( $22.0 \pm 4.91$  dB,  $p = 0.002$ ), and 12 ( $23.4 \pm 3.75$  dB,  $p < 0.001$ ) in the 1 + PRN group and from baseline ( $15.4 \pm 5.88$  dB) to months 1 ( $21.5 \pm 4.85$  dB,  $p = 0.003$ ), 3 ( $23.9 \pm 3.81$  dB,  $p = 0.002$ ), and 6 ( $22.3 \pm 4.51$  dB,  $p = 0.011$ ) in the 3 + PRN group but not from baseline to month 12 ( $20.9 \pm 8.56$  dB;  $p = 0.092$ ) in the 3 + PRN group (Figure 3a). There was no significant difference between the two groups at month 1, 3, 6, or 12 ( $p = 0.935$ ,  $p = 0.322$ ,  $p = 0.885$ , and  $p = 0.398$ , respectively). Moreover, mean macular sensitivity in the central 3 mm field also significantly improved from baseline ( $17.1 \pm 4.87$  dB) to months 1 ( $23.2 \pm 3.60$  dB,  $p < 0.001$ ), 3 ( $23.9 \pm 2.95$  dB,  $p < 0.001$ ), 6 ( $24.0 \pm 3.45$  dB,  $p < 0.001$ ), and 12 ( $25.0 \pm 3.01$  dB,  $p < 0.001$ ) in the 1 + PRN group and from baseline ( $17.5 \pm 5.75$  dB) to months 1 ( $22.7 \pm 5.18$  dB,  $p = 0.002$ ), 3 ( $24.0 \pm 4.34$  dB,  $p = 0.004$ ), and 6 ( $22.6 \pm 5.19$  dB,  $p = 0.031$ ) in the 3 + PRN group, but not from baseline to month 12 ( $21.6 \pm 7.57$  dB;  $p = 0.181$ ) in the 3 + PRN group (Figure 3b). There was no significant difference between the two groups at month 1, 3, 6, or 12 ( $p = 0.802$ ,  $p = 0.960$ ,  $p = 0.467$ , and  $p = 0.193$ , respectively). Lastly, mean macular sensitivity significantly improved in the central 6 mm field from baseline ( $18.6 \pm 4.33$  dB) to months 1 ( $23.3 \pm 3.04$  dB,  $p < 0.001$ ), 3 ( $24.0 \pm 2.63$  dB,  $p < 0.001$ ), 6 ( $24.0 \pm 2.94$  dB,  $p < 0.001$ ), and 12 ( $24.8 \pm 2.74$  dB,  $p < 0.001$ ) in the 1 + PRN group and from baseline ( $18.7 \pm 5.80$  dB) to months 1 ( $22.7 \pm 5.39$  dB,  $p = 0.007$ ), 3 ( $23.5 \pm 4.99$  dB,  $p = 0.009$ ), and 6 ( $22.5 \pm 5.36$  dB,  $p = 0.047$ ) in the 3 + PRN group, but not from baseline to month 12 ( $21.5 \pm 6.91$  dB;  $p = 0.264$ ; Figure 3c) in the 3 + PRN group. There was no significant difference between the two groups at month 1, 3, 6, or 12 ( $p = 0.759$ ,  $p = 0.772$ ,  $p = 0.429$ , and  $p = 0.168$ , respectively).



**Figure 3.** Comparison of the changes in macular sensitivity between groups receiving 1 or 3 initial intravitreal injections of an anti-vascular endothelial growth factor agent followed by pro re nata dosing (1 + PRN and 3 + PRN, respectively). Both groups showed improvement in macular sensitivity (1 + PRN, solid line; 3 + PRN, dashed line). (a) Central 1 mm field; (b) central 3 mm field; and (c) central 6 mm field. There was no significant difference between the 2 groups in any of the fields at any of the study visits. \*  $p < 0.01$  vs. baseline, \*\*  $p < 0.05$  vs. baseline.

We examined whether BCVA and macular sensitivity at month 12 were associated with patient and clinical characteristics, including age, duration of macular edema, baseline BCVA, baseline CMT, number of injections, and treatment regimen (1 + PRN vs. 3 + PRN; Table 2). In the logistic regression analysis, the treatment regimen showed no association at month 12 with either BCVA ( $p = 0.346$ ) or macular sensitivity within the central 1 mm, 3 mm, and 6 mm fields ( $p = 0.404$ ,  $p = 0.197$ , and  $p = 0.170$ , respectively). In multiple regression analysis, the number of injections ( $p = 0.043$ ) was associated with BCVA at month 12. Duration of macular edema was associated with macular sensitivity within the central 1 mm field at month 12 ( $p = 0.008$ ), and age was associated with macular sensitivity in the central 3 mm and 6 mm fields at month 12 ( $p = 0.043$  and  $p = 0.034$ , respectively).

**Table 2.** Factors associated with best-corrected visual acuity and macular sensitivity at month 12 in eyes treated with intravitreal ranibizumab injections for macular edema in central retinal vein occlusion.

| Variable                                           | Univariate              |                | Multivariate Stepwise   |                |
|----------------------------------------------------|-------------------------|----------------|-------------------------|----------------|
|                                                    | Correlation Coefficient | <i>p</i> Value | Correlation Coefficient | <i>p</i> Value |
| <b>BCVA at month 12</b>                            |                         |                |                         |                |
| Age (yrs)                                          | −0.05                   | 0.834          |                         |                |
| Duration of macular edema (days)                   | 0.18                    | 0.463          |                         |                |
| Baseline BCVA (log MAR)                            | −0.18                   | 0.459          |                         |                |
| Baseline CMT (μm)                                  | −0.25                   | 0.285          |                         |                |
| Number of injections                               | 0.45                    | 0.043          | 0.45                    | 0.043          |
| Treatment regimen (1 + PRN vs. 3 + PRN)            | 0.23                    | 0.346          |                         |                |
| <b>Macular sensitivity within 1 mm at month 12</b> |                         |                |                         |                |
| Age (yrs)                                          | −0.41                   | 0.073          |                         |                |
| Duration of macular edema (days)                   | −0.57                   | 0.008          | −0.57                   | 0.008          |
| Baseline BCVA (log MAR)                            | −0.04                   | 0.861          |                         |                |
| Baseline CMT (μm)                                  | −0.41                   | 0.073          |                         |                |

Table 2. Cont.

| Variable                                           | Univariate              |         | Multivariate Stepwise   |         |
|----------------------------------------------------|-------------------------|---------|-------------------------|---------|
|                                                    | Correlation Coefficient | p Value | Correlation Coefficient | p Value |
| Number of injections                               | −0.36                   | 0.117   |                         |         |
| Treatment regimen (1 + PRN vs. 3 + PRN)            | −0.20                   | 0.404   |                         |         |
| <b>Macular sensitivity within 3 mm at month 12</b> |                         |         |                         |         |
| Age (yrs)                                          | −0.45                   | 0.043   | −0.45                   | 0.043   |
| Duration of macular edema (days)                   | −0.43                   | 0.058   |                         |         |
| Baseline BCVA (log MAR)                            | −0.10                   | 0.680   |                         |         |
| Baseline CMT ( $\mu\text{m}$ )                     | −0.37                   | 0.115   |                         |         |
| Number of injections                               | −0.37                   | 0.114   |                         |         |
| Treatment regimen (1 + PRN vs. 3 + PRN)            | −0.30                   | 0.197   |                         |         |
| <b>Macular sensitivity within 6 mm at month 12</b> |                         |         |                         |         |
| Age (yrs)                                          | −0.47                   | 0.034   | −0.47                   | 0.034   |
| Duration of macular edema (days)                   | −0.33                   | 0.164   |                         |         |
| Baseline BCVA (log MAR)                            | −0.10                   | 0.684   |                         |         |
| Baseline CMT ( $\mu\text{m}$ )                     | −0.31                   | 0.181   |                         |         |
| Number of injections                               | −0.33                   | 0.156   |                         |         |
| Treatment regimen (1 + PRN vs. 3 + PRN)            | −0.32                   | 0.170   |                         |         |

BCVA = best-corrected visual acuity; CMT = central macular thickness; log MAR = logarithm of the minimum angle of resolution; PRN = pro re nata.

No serious ocular or non-ocular complications associated with IRI were observed in any of the eyes over the entire observational period. Additionally, no cases of conversion to ischemic type CRVO occurred.

#### 4. Discussion

To date, no other study has compared macular sensitivity after a single initial injection and three initial monthly injections of an anti-VEGF agent to treat macular edema secondary to CRVO. In this study, macular sensitivity significantly improved in the central 1 mm, 3 mm, and 6 mm fields from baseline to months 1, 3, 6, and 12 in the 1 + PRN group and from baseline to months 1, 3, and 6 in the 3 + PRN group, but not from baseline to month 12 in the 3 + PRN group. It may not have improved at month 12 in the 3 + PRN group because fewer eyes in this group required no PRN injections (1 + PRN, 4/11 [36.4%] vs. 3 + PRN, 2/9 [22.2%]) and because the mean age was approximately 7 years higher than that in the 1 + PRN group. Thus, the results of the multiple regression analysis support a decrease in age-associated macular sensitivity in the central 3 mm and 6 mm fields at month 12. However, we found no significant differences between the two regimens in macular sensitivity in the central 1 mm, 3 mm, and 6 mm fields at any of the follow-up examinations, indicating that treatment regimen is not associated with improvement in macular sensitivity, even at month 12.

The 1 + PRN group showed a significant improvement in BCVA from baseline to months 1, 3, 6, and 12, but the 3 + PRN group showed a significant improvement only at month 1, 3, and 12 and not at month 6. This difference is probably because more patients had recurrence of macular edema at 6 months in the 3 + PRN group (1 + PRN, 2/11 [18.2%] vs. 3 + PRN, 3/9 [33.3%]). However, we found no significant differences in BCVA between the two regimens at any time point, and no association of either regimen with BCVA at month 12. This finding is in line with a study that found similar visual outcomes for the 1 + PRN and 3 + PRN regimens in CRVO [11]. In addition, although our results cannot be directly compared with those of previous extensive studies that used 6 initial monthly injections, the improvement in BCVA at 12 months in our study (18.0 letters) appears to



be larger than that in CRUISE (13.8 letters) [5] and in studies on the efficacy and safety of VEGF trap-eye (i.e., intravitreal aflibercept injections) in CRVO (GALILEO; 16.9 letters [19], and COPERNICUS, 16.2 letters [20]). However, visual acuity may have been better in the present study because we excluded ischemic type CRVO.

Interestingly, multiple regression analysis showed that the duration of macular edema was associated with macular sensitivity in the central 1 mm field at month 12, meaning that the longer the duration of macular edema, the lower the macular sensitivity within the central 1 mm field. Macular sensitivity within this field may reflect the function of the fovea. These findings indicate that it might be advisable to start anti-VEGF therapy earlier in case of macular sensitivity.

Macular sensitivity is associated with retinal structure and can help to predict BCVA after anti-VEGF treatment [21]. Research is also examining the use of deep learning for predicting macular sensitivity and retinal function from structural OCT scans [22]. The aim is to assess visual function indirectly by analyzing structural-imaging findings and to develop feasible methods for use in clinical settings. Therefore, in the future, assessment of macular sensitivity may be useful for evaluating visual function in clinical trials and monitoring disease progression in patients.

This study has several limitations. First, the number of patients was small. Furthermore, the assignment of patients to the two regimen groups was not randomized; however, we suggest that the potential bias associated with this approach may be small because patients were consecutively enrolled by applying the same inclusion and exclusion criteria and because baseline clinical characteristics, including BCVA and CMT, were not significantly different between the two groups. In addition, it is unclear whether the efficacy of the 1 + PRN and 3 + PRN regimens is similar to that of the 6 + PRN regimen often used in previous randomized clinical trials. Therefore, future randomized controlled trials are warranted to confirm these results and compare treatment outcomes with 1 + PRN, 3 + PRN, and 6 + PRN regimens.

## 5. Conclusions

We found no significant differences in macular sensitivity in the central 1 mm, 3 mm, or 6 mm fields or in BCVA and CMT at 1, 3, 6, and 12 between the two groups and no association of treatment regimen with either BCVA or macular sensitivity within the central 1 mm, 3 mm, and 6 mm at month 12. These findings suggest that, in patients with CRVO and macular edema, a 1 + PRN regimen improves macular sensitivity, BCVA, and CMT to a similar extent as a 3 + PRN regimen does.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants and because ethics committee approval for release of the data was not obtained.

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