

# High-dose aflibercept injection has striking effects on myopic choroidal neovascularization

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**Abstract.** The aim of the present study was to evaluate the 1-year outcomes of a high-dose aflibercept injection [4 mg 2+ pro re nata (PRN) scheme] for individuals with myopic choroidal neovascularization (mCNV) through optical coherence tomography (OCT) follow-ups. A total of 16 consecutive patients (7 males and 9 females; sixteen eyes) with mCNV were enrolled in this retrospective study. The mean age was  $30.5\pm 3.35$  years and mean spherical equivalent was  $-7.31\pm 0.90$  D. Subjects received 4 mg aflibercept intravitreal injection on the day of diagnosis and 35 days later. Further injections of aflibercept were required when the following were detected by OCT and fluorescein angiography: i) Decrease in best corrected visual acuity (BCVA); ii) aggravation of metamorphopsia; iii) macular oedema; iv) macular haemorrhage; v) increase in retinal thickness; and vi) leakage. Ophthalmic examination and OCT were performed at the baseline, as well as at 1, 2, 4, 6, 8, 10 and 12 months after the initial aflibercept injection. BCVA and central retinal thickness (CRT) were evaluated at each follow-up. The results showed that the vision of all subjects improved following the aflibercept intravitreal injection. The mean BCVA improved from  $0.35\pm 0.15$  logarithm of the minimal angle of resolution (logMAR) at the baseline to  $0.12\pm 0.05$  logMAR at final follow-up ( $P<0.05$ ). A reduction in metamorphopsia was observed and the mean CRT

was reduced from  $345.38\pm 34.69$   $\mu\text{m}$  of pre-treatment levels to  $222.75\pm 8.98$   $\mu\text{m}$  at the last postoperative visit ( $P<0.05$ ). The mean number of injections in the present study was  $2.13\pm 0.5$ . Out of all patients, 13 received two injections and 3 subjects received three injections. The mean follow-up was  $13.41\pm 1.17$  months. Based on the outcomes, it was found that an intravitreal injection of high-dose aflibercept (4 mg 2+PRN scheme) is effective for vision improvement and stabilization. In addition, it also significantly alleviated metamorphopsia and reduced the CRT in patients treated with mCNV. During the follow-up, the eyesight of the patients was stable.

## Introduction

Patients with a refractive error of  $<-6$  degrees or an axial length of  $>26.5$  mm and typical pathological changes in the fundus are diagnosed with pathologic myopia (PM). PM occurs in 1-3% of adults (1,2). Certain phenotypic features of PM, including patchy atrophy, the thinning of choroid and choriocapillaris, lacquer cracks and choroidal neovascularization (CNV) in the fellow eye may increase the risk of myopic CNV (mCNV) (3-5). In addition, CNV has been reported to be a vision-threatening complication in 5.2-10.2% of highly myopic eyes (6).

In recent years, the anti-vascular endothelial growth factor (VEGF) agents used in patients with mCNV have demonstrated considerable success in visual acuity gains and have led to an improvement in the patients' quality of life (7). Intravitreal and subtenon steroids, photodynamic therapy, transpupillary thermotherapy and various other treatments have had varying degrees of success in preventing visual loss in patients with CNV (8,9). Due to the good efficacy of anti-VEGF biological agents, including bevacizumab, ranibizumab and aflibercept, these have been proposed as a first-line treatment for mCNV (10). The visual prognosis and natural progression of mCNV are more favourable than those of CNV secondary to age-related macular degeneration (AMD) and patients with mCNV have shown a good response to anti-VEGF therapy (11).

Bevacizumab and ranibizumab, which are respectively a whole anti-VEGF antibody and an antibody fragment, have been mostly used in mCNV treatment targeting VEGF-A, according to studies conducted after 2006 (12,13). Aflibercept is a new recombinant fusion protein consisting of a homodimeric

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*Abbreviations:* OCT, optical coherence tomography; mCNV, myopic choroidal neovascularisation; PM, pathologic myopia; BCVA, best-corrected visual acuity; anti-VEGF, anti-vascular endothelial growth factor; AMD, age-related macular degeneration; CRT, central retinal thickness; PRN, pro re nata

*Key words:* optical coherence tomography, anti-vascular endothelial growth factor, pathologic myopia, choroidal neovascularization, aflibercept

glycoprotein formed by the fusion of the extracellular domain of human VEGF receptor (extracellular domain 2 of VEGF receptor 1 and extracellular domains 3 and 4 of VEGF receptor 2) and the Fc portion of human immunoglobulin G1 (14). It has high affinity for placental growth factors and VEGF isoforms (15). The MYRROR study indicated that aflibercept is well-tolerated and effective in the treatment of mCNV. In this trial, patients in the intravitreal aflibercept group received two injections between weeks 0 and 8 (16). A recent study on the treatment of mCNV with different anti-VEGF agents pointed out that aflibercept was more effective to resolution of CNV activation and may be preferred to maintain anatomical and visual yields in eyes with PM for longer follow-ups (17).

Studies on high-dose anti-VEGF therapy used to treat neovascular AMD have been conducted. Broadhead *et al* (18) found that higher dose anti-VEGF therapy may obtain improved anatomic outcomes and maintain vision, but frequent injections are required to achieve this. Another study by You *et al* (19) suggested that an intravitreal aflibercept injection at a high dose and frequency is an effective treatment for patients with wet AMD. Nguyen *et al* (20) reported that an intravitreal injection of 4 mg aflibercept is safe and well-tolerated. In the same study, the 4-mg dose significantly reduced foveal thickening, improved best corrected visual acuity (BCVA) and reduced repeat injections in patients with neovascular AMD. Current studies on the use of aflibercept for the treatment of mCNV usually use a dose of 2 mg (16,21). To date, research on the use of high-dose aflibercept for mCNV has been limited.

The number of injections varies among different studies. In the study performed by Bruè *et al* (22), 68.4% of patients received one or two injections and 31.6% required three to five injections over the 18-month follow-up. Another study indicated that BCVA improvement was achieved with a median of two injections and was sustained for up to 12 months (21). In the study by Korol *et al* (23), patients received a mean of 2.6 intravitreal injections over 12 months. Based on previous studies (18,19) and our experience, a 4 mg [2+ pro re nata (PRN) scheme] aflibercept injection was selected in the present study to observe the outcomes for patients with mCNV for 12 months of follow-up and to compare the present results with those of other studies.

## Patients and methods

**Patients.** This retrospective study reviewed the charts of patients with mCNV encountered at the Central Hospital Affiliated to Shandong First Medical University (Jinan, China) between January 2019 and August 2021. A total of 16 consecutive subjects (7 males and 9 females; age range, 26-38 years) with mCNV were enrolled in this retrospective study. The study was approved by the ethics committee of the Central Hospital Affiliated to Shandong First Medical University (Jinan, China; approval no. 2022-130-01) and was performed according to the Declaration of Helsinki. All subjects provided written informed consent prior to treatment. CNV was diagnosed by clinical examination, optical coherence tomography (OCT; Cirrus HD-OCT 4000; Carl Zeiss Meditec, Inc.) and fluorescein angiography (FA) and/or

indocyanine angiography. All patients underwent computerized optometry using a Topcon KR-800 (Beijing Dakang Instrument Co., Ltd.), axial length measurement (IOLMaster<sup>®</sup>; Carl Zeiss AG) and intraocular pressure (TOPCON CT-800). The inclusion criteria were as follows: i) High myopia with a refractive error of <-6 diopters; ii) axial length of >26.5 mm; iii) myopic retinal pathological changes (posterior staphyloma, chorioretinal atrophy, papillary crescent and lacquer cracks); iv) OCT evidence of hyperreflective lesion; v) FA detection of subfoveal active CNV; and vi) BCVA of  $\geq 0.5$  logMAR prior to treatment. The exclusion criteria were as follows: i) Patients with different macular diseases, such as ARMD and diabetic macular oedema; ii) patients with previous subfoveal or juxtafoveal laser treatment; iii) history of trauma; iv) ophthalmic surgery; v) presumed ocular histoplasmosis syndrome; vi) hereditary eye disease; and vii) any other cause of secondary CNV or spheric equivalent, such as astigmatism.

**Treatments and follow-up.** All patients received an intravitreal injection of 4 mg aflibercept (Bayer AG). The lids and conjunctiva were disinfected with 10% iodophor and 5% povidone iodine, respectively. The conjunctiva was anesthetized with 1% oxybuprocaine. Aflibercept (4 mg) was injected using a 30-g needle through the pars plana (4 mm from the limbus of the phakic eye) into the vitreous and an eye patch was placed over the eye following treatment. Gatifloxacin eye drops (China Otsuka Pharmaceutical Co., Ltd.) were prescribed to be instilled four times a day for 7 days, starting on the second day after surgery. The second injection was administered 35 days later. Ophthalmic examination and OCT were performed at the baseline and at 1, 2, 4, 6, 8, 10 and 12 months after the initial injection. At each follow-up visit, a thorough ophthalmic assessment was performed, including an evaluation of BCVA and retinal morphology with OCT. FA was performed if the activity of the lesion could not be estimated by clinical expression and OCT assessment at each follow-up visit. BCVA, macular appearance, OCT and FA findings were used to decide if the subject should have received another intravitreal injection of aflibercept. A decrease in BCVA, aggravation of metamorphopsia, presence of macular oedema or haemorrhage, increased central retinal thickness (CRT) or central macular thickness (CMT), or increased leakage created the need for additional treatment with aflibercept.

**Statistical analysis.** Statistical analysis using SPSS version 26.0 (IBM Corp.). All values in the text are presented as the mean  $\pm$  standard deviation. The outcomes at different time-points following treatment were compared with baseline values of BCVA and CRT individually. Pairwise comparisons were performed at different postoperative time-points. The data were evaluated for normality using normality tests. Normally distributed data were assessed using repeated-measures ANOVA and pairwise comparisons were performed using Friedman's test. Homogeneity of variance was tested prior to ANOVA. Non-normally distributed data were assessed using the Kruskal-Wallis H-test. Dunn's test was used for pairwise comparisons.  $P < 0.05$  was considered to indicate a statistically significant difference.

Table I. Baseline demographic and clinical characteristics (patients, n=16; eyes, n=16).

Characteristic	Value
Gender	
Male	7
Female	9
Age, years	30.5±3.35
Spherical equivalent, D	-7.31±0.90
Axial length, mm	27.17±0.89
Duration of symptoms, months	0.96±0.67
Number of injections	2.13±0.5
Follow-up duration, months	13.41±1.17

Data are presented as n or mean ± standard deviation.

## Results

**Patient disposition, baseline characteristics and exposure.** All 16 eyes were administered an aflibercept intravitreal injection. Basic information of the two groups is provided in Table I. Follow-up images were obtained at 1, 2, 4, 6, 8, 10 and 12 months after treatment. None of the patients developed glaucoma following the high-dose aflibercept injection and intraocular pressure (IOP) in all eyes was controlled at <21 mmHg at each visit. During the follow-up period, no cardiovascular or cerebrovascular embolism and no death events were recorded.

**Key outcomes.** The Snellen BCVA was changed into a logarithm of the minimum angle of resolution (logMAR). The changes in BCVA and CRT reached statistical significance at the 1-, 2-, 4-, 6-, 8-, 10- and 12-month follow-ups compared with the baseline. The mean BCVA improved from 0.35±0.15 logMAR at the baseline to 0.12±0.05 logMAR at the final follow-up (P<0.05; Fig. 1). The reduction in metamorphopsia was obvious. The mean CRT at the last follow-up was reduced from 345.38±34.69 μm (pre-treatment levels) to 222.75±8.98 μm (P<0.05; Fig. 2). There was a significant difference in BCVA at 12 months after surgery compared with the 1-month follow-up (P<0.05). There were significant differences in CRT at the 2-, 4-, 6-, 8-, 10- and 12-month follow-ups, as compared with the 1-month follow-up after the initial injection (P<0.05). In addition, significantly different changes were observed at 4-months of follow-up compared with the 2-month follow-up. Most of the retinal fluid was absorbed and the choroidal neovascularization was diminished within the subretinal space. The favourable results of the present study strengthened the confidence in the efficacy of high-dose aflibercept for mCNV treatment.

**Case of a patient.** Fig. 3A-G presents the changes in the OCT scan of a representative patient (female, 29 years old) diagnosed with mCNV during the follow-up. At diagnosis, OCT indicated fibrovascular pigment epithelial detachment and increased retinal thickness in the fovea. The BCVA was 0.9 logMAR. At one month after the initial injection, the fibrovascular pigment

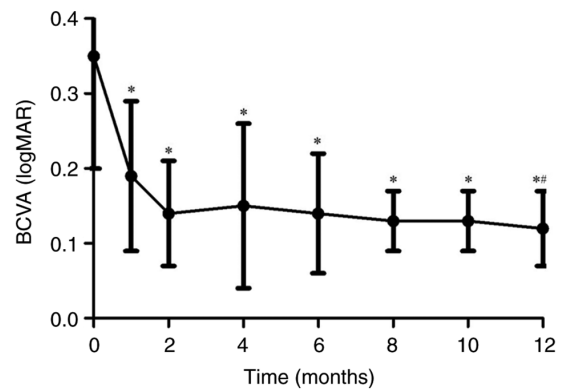


Figure 1. BCVA changes following treatment with high-dose aflibercept. BCVA was significantly improved after treatment and remained stable during the 12-month follow-up. \*P<0.05 vs. baseline. #P<0.05 vs. 1 month. BCVA, best-corrected visual acuity.

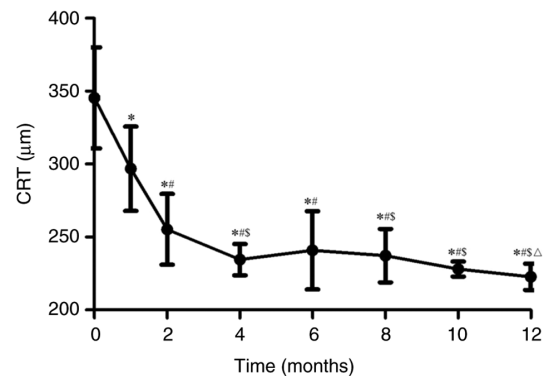


Figure 2. CRT changes following treatment with high-dose aflibercept. The CRT decreased significantly in the first 4 months after treatment and remained stable until the end of the 12-month follow-up. \*P<0.05 vs. baseline; #P<0.05 vs. 1 month; \$P<0.05 vs. 2 months; and ΔP<0.05 vs. 6 months. CRT, central retinal thickness.

epithelial detachment had partially retreated and the retinal thickness decreased from 341 μm (pre-treatment levels) to 221 μm. A strong dot reflection may be seen at the top. The BCVA was 0.4 logMAR. After the second aflibercept 4 mg injection, the OCT scan showed that the neovascularization further retreated. It was observed that the neovascularization gradually subsided, the retinal thickness returned to normal, the morphology of the macular fovea was almost normal in late follow-ups and the BCVA was improved and stable. The BCVA was 0.3, 0.3, 0.2, 0.1 and 0.1 logMAR at 2, 4, 6, 8 and 12 months, respectively, following the initial aflibercept injection (data not shown).

## Discussion

mCNV is one of the sight-threatening complications of PM. The application of anti-VEGF drugs in choroidal neovascularization of high myopia has markedly improved the visual quality of patients, particularly the working population. Among the anti-VEGF drugs, bevacizumab and ranibizumab exhibited a similar efficacy in restoring functional and anatomical parameters. However, ranibizumab was designed and approved for ocular administration. It appears to be the preferred

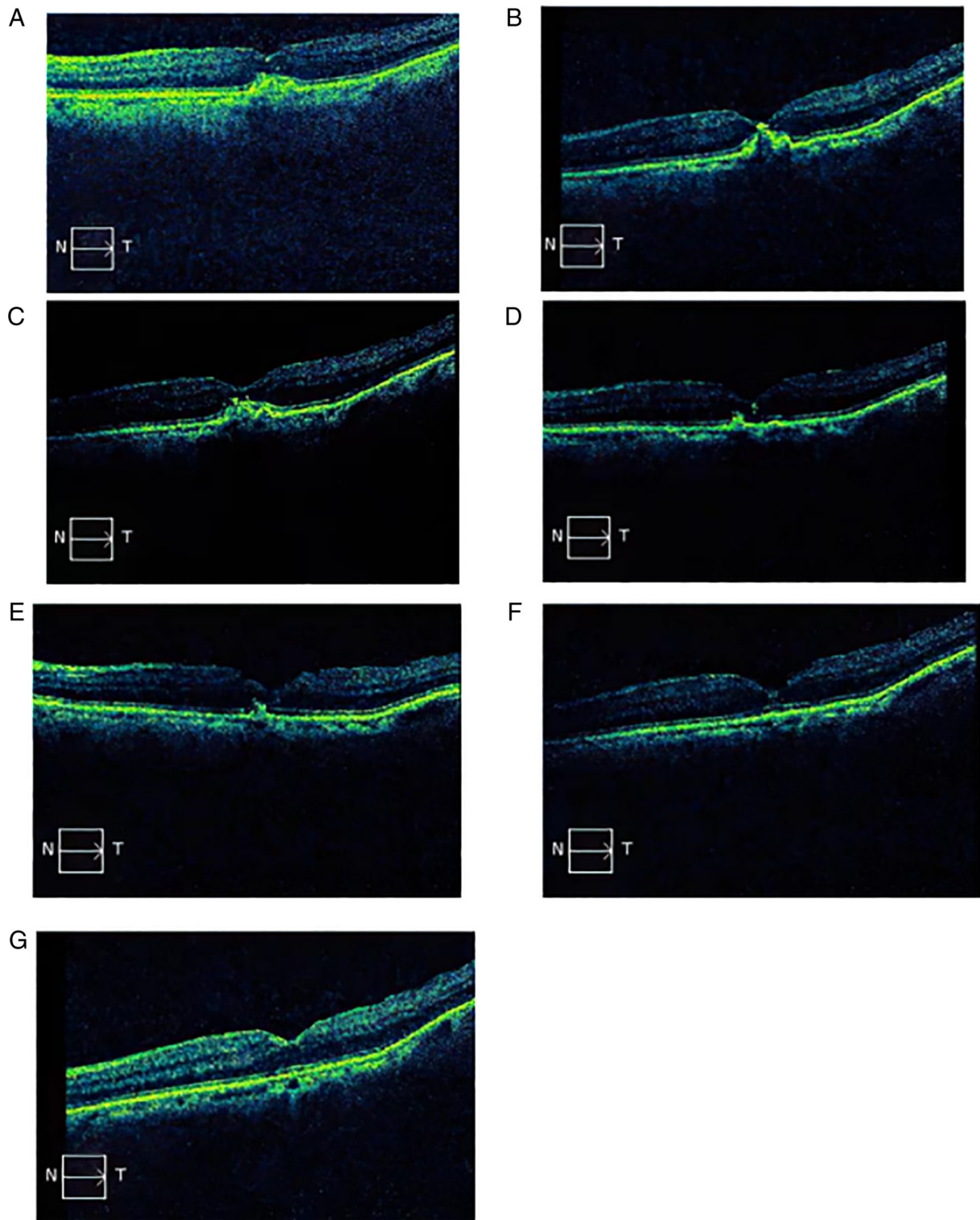


Figure 3. OCT changes of a representative patient diagnosed with myopic choroidal neovascularization during the follow-up. (A) At diagnosis, OCT indicated fibrovascular pigment epithelial detachment and increased retinal thickness in the fovea. (B) At 1 month after the initial injection, OCT revealed that the fibrovascular pigment epithelial detachment partially retreated and the retinal thickness decreased. A strong dot reflection is seen at the top. OCT at (C) 2, (D) 4, (E) 6, (F) 8 and (G) 12 months after initial aflibercept injection. The distance of pigment epithelial detachment gradually decreased until it returned to normal. The magnification was 1:1. OCT, optical coherence tomography; N, nasal; T, temporal.

treatment for mCNV, as it achieves efficacy with a short treatment duration and frequency and few adverse effects (10,23). Aflibercept as a new generation of anti-VEGF agent was originally approved for the treatment of AMD. Fauser and Muether compared the VEGF suppression times in their study on AMD

treatment and reported that aflibercept has significantly longer VEGF suppression times compared with ranibizumab (24).

There is now substantial evidence in favour of the use of aflibercept for mCNV. Toto *et al* (7) reported the most recent data from the articles of anti-VEGF therapy for mCNV. In

their study on intravitreal aflibercept injection for mCNV, Chen *et al* (25) found that a single aflibercept 2.0 mg injection resolved mCNV in ~50% of the patients. The median number of injections was two within 12 months. Another prospective 12-month cohort study reported promising results; the efficacy of the intravitreal aflibercept (2 mg) 2+PRN regimen in 31 eyes of 30 patients with mCNV was evaluated and the mean decimal BCVA improved from 0.2±0.1 at the baseline to 0.35±0.16 at the 12-month follow-up (23). In addition, studies showing the efficacy of the initial dosing regimens, such as the 1+PRN and 3+PRN regimens, indicated no statistically significant difference in BCVA. In a retrospective study, Kung *et al* (26) reported that there was no significant difference in visual improvement between the eyes with a single intravitreal injection and the eyes with a loading dose of 3 monthly injections. The mean number of injections was 2.32 and 3.57, respectively. Korol *et al* (27) reported a series of 47 eyes with 24-month follow-up in which there was an increase in BCVA and decrease in central foveal thickness. The total mean number of injections in their study was 2.8±1.1. In another study by our group on mCNV treatment using conbercept, it was found that the effect of one injection was not ideal; the CRT was 261.50±21.66  $\mu\text{m}$  at 1 month after the first injection and 247.06±23.85  $\mu\text{m}$  at 1 month after the second injection (28). Furthermore, the mean CNV area was 0.22 mm<sup>2</sup> at 1 month after the first injection and was 0.07 mm<sup>2</sup> at 1 month after the second injection.

The outcomes of 16 consecutive eyes with mCNV treated with 4 mg aflibercept intravitreal injection were retrospectively reviewed and followed up for 12 months. All eyes initially underwent two injections 35 days apart, followed by an additional injection based on monthly visits. The present study revealed several clinical effects of the intravitreal injection of aflibercept in the treatment of mCNV. The BCVA improved from 0.35±0.15 logMAR at the baseline to 0.12±0.05 logMAR at the final follow-up visit. The BCVA improved significantly 1 month after the initial injection and further after the second injection. There was a significant difference in BCVA at 1 and 12 months after surgery. An ideal visual acuity was achieved and remained stable after two injections. The CRT was decreased significantly from 345.38±34.69 to 296.88±28.93  $\mu\text{m}$  at 1 month after the initial injection. At 2 months after treatment, the CRT reached 255.31±24.25  $\mu\text{m}$ . At 4 months from surgery, the CRT was further reduced and reached 234.56±10.74  $\mu\text{m}$ . The CRT remained stable and was 222.75±8.98  $\mu\text{m}$  at the 12-month follow-up visit. In the present study, the CRT reached stable levels at 2 and 4 months after the initial injection. This outcome is different from what was previously reported in the MYRROR trial (16). The MYRROR trial, which adopted an as-needed aflibercept treatment for mCNV, indicated that the CMT rapidly decreased and reached stable levels between weeks 4 and 8. Such an early improvement of CMT was consistent with another retrospective clinical study, which compared bevacizumab to aflibercept in the treatment of mCNV (29). At week 48, in the MYRROR trial, the decrease in CRT was 86.2  $\mu\text{m}$ , whereas in the present study, it was 122.63  $\mu\text{m}$  (16). Furthermore, in the present study, aflibercept had significant advantages in terms of the VEGF suppression times in the treatment of mCNV. Only 3/16 mCNV cases were injected for the third time and the mean number of injections

during the 12-month follow-up was 2.13±0.5, which was lower than that in other studies (23,26,27,30). In the present study, it was found that the 4 mg aflibercept 2+PRN scheme was able to markedly eliminate neovascularization. In addition, none of the cases had any recurrence or significant increase in CRT, while the visual acuity remained stable during the 12-month follow-up. The present results showed that aflibercept may represent an ideal choice for mCNV treatment. Following the diagnosis of mCNV, a timely intravitreal injection of aflibercept may provide an improved curative effect.

As with any common intraocular surgery, intravitreal injections of anti-VEGF drugs are accompanied by risks of bleeding, infection, cataracts and glaucoma (31). Elevated IOP and ocular inflammation following intravitreal injection are the most frequently reported serious ocular adverse events (32). Therefore, a comprehensive ophthalmic examination should be performed in subjects with mCNV prior to intravitreal injections. In the present study, no systemic or ocular safety issues were noted in any of the patients treated with high-dose aflibercept. No cases of increased IOP or intraocular inflammation were noted in patients treated with 4 mg aflibercept. The safety and efficacy of high-dose therapy for mCNV needs to be confirmed by large-scale and rigorous clinical trials.

There were several limitations to the present study that may impact or influence the interpretation and generalizability of the findings. First, due to the retrospective design, the lack of randomization somewhat reduced the power of the results. Furthermore, the outcomes should be interpreted with caution due to the small sample size. As another limitation, the study lacked a control group. In addition, the follow-up time was short (12 months) and continuous follow-up is necessary. The present study also has its advantages. To the best of our knowledge, this is the first clinical observation obtained using high-dose aflibercept (4 mg) in the treatment of mCNV. According to these results, the 4 mg aflibercept 2+PRN scheme proved effective for mCNV, but future studies, require to be conducted in order to further evaluate the effect of this scheme.

In conclusion, the present study indicated that an intravitreal injection of high-dose aflibercept (4 mg 2+PRN scheme) was effective in promoting vision improvement and stabilization. It also significantly alleviated metamorphopsia and reduced the CRT in patients with mCNV. During the 12-month follow-up, the BCVA and CRT were stable. The present results suggested that the aflibercept 4 mg 2+PRN scheme may be an ideal choice for mCNV treatment, prompting further studies to evaluate the effect of this regimen.

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#### Availability of data and materials

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

### Authors' contributions

WZ and CH designed the study and drafted and revised the manuscript. YH and ZY performed data acquisition, analysis and interpretation. All authors have read and approved the final manuscript. CH and WZ confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Central Hospital Affiliated to Shandong First Medical University (Jinan, China; approval no. 2022-130-01). Written informed consent was obtained from all patients.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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