• Clinical Research •

Long-term clinical effects of intravitreal injections of conbercept for the treatment of choroidal neovascularization in patients with pathological myopia

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Abstract

● **AIM:** To observe the long-term clinical efficacy of intravitreal injections of conbercept, a novel vascular growth factor inhibitor, for the treatment of pathological myopia choroidal neovascularization (PM-CNV).

● **METHODS:** A total of 67 eyes (from 67 patients; mean age, 54.90±12.7y) with PM-CNV were retrospectively researched. Based on the different schemes used for the administration of the drug, the patients were divided into two groups: group A (*n*=35; average age, 53.31±13.6y; average diopter, 9.25±1.72 D), which received only one injection of *pro re nata* (PRN; 1+PRN regimen), and group B (*n*=32; average age, 56.49±11.8y; average diopter, 9.63±2.24 D), which received one injection per month for 3mo (3+PRN regimen). Best-corrected visual acuity (BCVA) analysis, intraocular pressure (IOP) examination, slit-lamp microscopy, fundus examination and optical coherence tomography were performed at each follow-up. The recurrence and treatment times of CNV were recorded. The patients were followed up for at least 12mo.

● **RESULTS:** The BCVA was increased in 29 eyes (82.9%) in group A and 30 eyes (93.75%) in group B; no increase or decrease was observed in 6 (17.1%) and 2 (6.25%) eyes in groups A and B, respectively. The BCVA (logMAR) values before treatment (0.67±0.48 and 0.71±0.56) were significantly higher than those 12mo after treatment (0.31±0.26 and 0.33±0.17) in groups A and B, respectively (*P*<0.05). The mean central macular thickness (CMT) values had significantly decreased from 346.49±65.99 and 360.10±82.31 μm at baseline to 257.29±40.47 and 251.97±48.26 μm in groups A and B, respectively, after 12mo of treatment. A total of 21 eyes in group A needed reinjection (60%; average number of injections, 2.51±0.98); the corresponding values in group B were 6 eyes (18.75%; average number of injections, 3.74±1.22). There were no adverse ocular and systemic complications during the treatment and follow-up.

● **CONCLUSION:** Intravitreal injection of conbercept with 1+PRN or 3+PRN improve the visual acuity, reduce macular edema and reduce the level of CMT in patients with PM-CNV. The 3+PRN regimen demonstrates a lower recurrence rate of CNV than the 1+PRN regimen, but requires more treatment. However, both treatment regimens demonstrate long-term safety and efficacy for the treatment of PM-CNV.

● **KEYWORDS:** pathological myopia; choroidal neovascularization; conbercept; best-corrected visual acuity; central macular thickness

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INTRODUCTION

The incidence rate of myopia continues to increase year by year worldwide due to the changes in lifestyle and working style and the extension of the time of close eye use. In East Asia and Southeast Asia, 95% of the population require glasses or contact lenses to enable clear vision beyond arm's length[1]. Currently, the prevalence of myopia is more than 80% among university students in China. Uncorrected myopia is not only among the leading causes of visual impairment and blindness, but if it progresses to high or pathological myopia (PM)[2]. In China, about one-fifth of the population (about 300 million people) is known to experience myopia, out of which 10 million people have PM. PM is a degenerative disease and the main cause of blindness among the working-age population worldwide[3]. It has been associated with

complications, such as myopic macular degeneration (MMD), retinal detachment (RD), cataract, and open angle glaucoma (OAG)[4]. Characteristics of MMD are lacquer cracks, Fuchs spot, choroidal neovascularization (CNV), or chorioretinal atrophy[5]. PM is the main cause of CNV (in individuals below 50 years of age)[6] and irreversible vision loss (in young people, particularly Asians)[7]. Between 5% and 11% of patients with PM will develop myopic CNV (mCNV)[8]. Yoshida *et al*[3] reported a decrease in visual acuity 5-10y after CNV; the proportion of best-corrected visual acuity (BCVA) was less than 0.1 in 89% and 96% of the patients after 5 and 10y, respectively. About 35% of patients with PM-CNV can present with binocular lesions within 8y. Therefore, patients with PM who present with secondary CNV require treatment immediately. The previous methods employed for the treatment of PM-CNV include laser photocoagulation, transpupillary thermotherapy and photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis AG, Bülach, Switzerland)[9]. However, long-term clinical observations indicated that the effect on the visual acuity of the patients was not ideal. Tong *et al*[10] examined the level of vascular endothelial growth factor (VEGF) in the vitreous and reported significantly higher levels in patients with PM-CNV when compared with the control group. The intravitreal injection of anti-VEGF drugs for the treatment of PM-CNV has achieved good clinical results, which resulted in improvements in the vision of the patients. Conbercept, a novel anti-VEGF drug developed in China, was the first to obtain approval from the China Food and Drug Administration (CFDA) for the treatment of PM-CNV. Conbercept is a recombinant soluble VEGF receptor protein, which was fabricated by fusing the second IG-like domain of VEGFR-1 and the third and fourth IG-like domains of VEGFR-2 to the Fc portion of human IgG1. It can bind to VEGF-A, VEGF-B, VEGF-C and placental growth factor (PlGF) with high affinity and a long half-life in the vitreous[11-14]. When compared with patients with wet age-related macular degeneration, those with PM-CNV have a relatively younger age of onset and obvious visual impairment, which seriously affects their daily work and life. Therefore, the safety and duration of the intravitreal injection of conbercept for the treatment of PM-CNV might have a significant impact on the lives of the patients. There is no clear consensus or guideline for the treatment of PM-CNV using anti-VEGF drugs; various administration schemes have been widely used in the clinical setting.

Thus, this retrospective study aimed to determine the long-term clinical efficacy of two administration schemes involving the intravitreal injection of conbercept for the treatment of PM-CNV.

SUBJECTS AND METHODS

Ethical Approval This study followed the guidelines of the Declaration of Helsinki and was approved by Ethics Commitee of Nanjing Drum Tower Hospital (2019-502-01). Informed consent was obtained from all the participants in the study.

Subjects and Groups This retrospective study included 67 eyes from 67 patients with PM-CNV who received intravitreal injection of conbercept in our hospital from January 2019 to October 2020. The average age of the patients was 54.90±12.7y; 20 eyes (from 20 males) and 47 eyes (from 47 females) were examined (Table 1). Based on the different initial administration schemes, the eyes were divided into two groups: group A comprised 35 eyes (from 35 patients; average age, 53.31±13.6y; average diopter, 9.25±1.72 D) treated with one injection of *pro re nata* (PRN; 1+PRN regimen), and group B comprised 32 eyes (from 32 patients; average age, 56.49±11.8y; average diopter, 9.63±2.24 D) treated with one injection per month for the first 3mo (3+PRN regimen). At each follow-up, BCVA analysis, intraocular pressure (IOP) examination, slit-lamp microscopy, fundus examination and optical coherence tomography (OCT) were performed. The results of BCVA and OCT, were detected, the recurrence and treatment times of CNV were recorded.

The patients were treated with the regime of 1+PRN or 3+PRN, 0.5 mg/0.05 mL of conbercept was injected into the vitreous cavity each time. The BCVA and OCT were recorded at 3, 6 and 12mo after the first treatment. The central macular thickness (CMT), IOP and fundus were measured. The decision to inject again was made based on the regression and activity of the neovascularization. All patients were regularly followed up for at least 12mo.

The inclusion criteria for this study were as follows: diopter <-6.00 D or axial length >0.26 mm, fundus fluorescein angiography (FFA) showing fluorescence leakage at the CNV in the macular area, OCT showing neovascular lesions in the macular area and no history of laser or PDT treatment. The exclusion criteria were as follows: refractive interstitial opacity during fundus examination; CNV lesions in the macular region due to other causes; RD; epiretinal membrane; glaucoma; uveitis; intraocular infectious lesions; lesions in the fundus caused by hypertension, diabetes and other systemic diseases; cardio-cerebrovascular infarction that has occurred within 6mo of the study; and the patients unable to follow-up on time.

Eye examination: All patients underwent BCVA before the intravitreal injection. The international standard logarithmic visual acuity chart, slit-lamp anterior segment and mydriasis fundus examination and IOP examinations were conducted.

Fluorescence angiography: All patients were examined using the Heidelberg confocal laser synchronous angiography camera (HRA, Germany). CNV was observed in the macular area along with fluorescence leakage.

Table 1 Baseline characteristics of choroidal neovascularization in patients with pathological myopia who were treated with intravitreal injections of conbercept

Characteristics	1+PRN	3+PRN	*P*
Number	35	32	-
Female, *n* (%)	26 (74.29)	21 (65.63)	0.439
Mean axial length (mm)	27.52±1.44	28.19±1.36	0.589
Age (y)	53.31±13.6	56.49±11.8	0.775
Mean refractive errors (diopters)	9.25±1.72	9.63±2.24	0.827
logMAR BCVA	0.67±0.48	0.71±0.56	0.274
CMT (μm)	346.49±65.99	360.10±82.31	0.834

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; PRN: *Pro re nata*.

OCT and OCTA (optical coherence tomography angiography) examinations: All patients were examined using the Heidelberg OCT and OCTA (Germany), and a CMT of 6×6 mm^2 was observed. Each follow-up examination was conducted by the same physician and in the same direction to track the changes in the CMT and the morphology of the neovascularization.

Surgical Methods For the preoperative preparation, 0.5% levofloxacin eye drops were applied to the eye 3d before the operation (four times a day). After routine disinfection, a topical anaesthetic (0.4% oxybuprocaine hydrochloride eye drops) was applied for 10min, followed by the injection of 0.5% povidone-iodine into the conjunctival sac. After allowing it to soak for 90s, the conjunctival sac was rinsed with 0.9% normal saline, and 0.5 mg/0.05 mL of the anti-VEGF drug (conbercept) was vertically injected 4 mm away from the limbus cornea, in the flat part of the ciliary body. The needle was pressed with a cotton swab. Refers to the measurement of IOP and asks whether the patient can see the manual clearly. In the absence of any adverse reaction, the conjunctival sac was coated with levofloxacin hydrochloride eye gel and covered with sterile gauze. After the procedure, prednisolone acetate eye drops and 0.5% levofloxacin eye drops were administered for 1wk.

Postoperative Follow-up All patients underwent BCVA, IOP measurement, fundus examination and OCT measurement at 3, 6 and 12mo after the initial treatment, OCT measurement focused on macula 6×6 mm^2 retinal thickness. During the recording, the international logarithmic vision was converted to logMAR vision. Patients who presented with an increase in BCVA or decrease in CMT after the first treatment entered the follow-up phase. Conbercept was reinjected into the vitreous cavity if the vision dropped by more than two lines, the FFA showed neovascular leakage, and OCT showed subretinal or intraretinal fluid and hemorrhage recurrence at macular area.

Statistical Analysis Statistical analyses were performed using a commercially available software (SPSS version 21.0 for Windows; SPSS Inc, Chicago, IL, USA). The measurement data were expressed as mean±standard deviation (SD). Comparisons of the BCVA and injection times between the two groups before and after treatment were performed using the Wilcoxon rank-sum test, whereas the paired sample *t*-test was used for the comparisons of the CMT before and after treatment. The independent sample *t*-test was used to compare the continuous variables between the groups. The counting data were expressed as *n*, and the categorical variables between the two groups were compared using the Chi-squared test. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Best-corrected Visual Acuity Before and After Treatment in the Two Groups As presented in Table 2, in group A, the baseline of BCVA (logMAR) was 0.67±0.28. BCVA increased in 29 eyes (82.9%) and did not increase or decrease in 6 eyes (17.1%) 3mo after first treatment. The values of BCVA at 3, 6 and 12mo after treatment were 0.34±0.19, 0.32±0.35 and 0.31±0.26, respectively. The BCVA at 12mo after treatment was significantly different (P<0.05) from that before treatment. In group B, the baseline of BCVA was 0.71±0.56. BCVA was increased in 30 eyes (93.75%), whereas no increase or decrease was observed in 2 eyes (6.25%) at 3mo after the first treatment. The BCVA values were 0.36±0.20, 0.33±0.23 and 0.33±0.17 at 3, 6 and 12mo after the first treatment, respectively. The BCVA at 12mo after treatment was significantly different (P<0.05) from that before treatment. No significant differences in BCVA were observed between the two groups at 3, 6 and 12mo.

Central Macular Thickness Before and After Treatment in the Two Groups In group A, the mean CMT at baseline was 346.49±65.99, and those at 3, 6 and 12mo after treatment were 280.17±54.36, 264.37±46.41 and 257.29±40.47, respectively (Table 2). The CMT at 3, 6 and 12mo after treatment was significantly different (9.877, 7.264 and 6.054, respectively; P<0.05) when compared with that before treatment. In group B, the mean CMT at baseline was 360.10±82.31, and those 3, 6 and 12mo after treatment were 292.63±75.20, 253.74±57.42 and 251.97±48.26, respectively. The differences in CMT at 3, 6 and 12mo after treatment were statistically significant (16.436, 7.401 and 5.50, respectively; P<0.05) when compared with that before treatment. No significant differences in CMT were observed between the two groups before treatment and at 3, 6 and 12mo after treatment.

Table 2 BCVA and CMT in the two groups before and after treatment after 12mo of follow-up

Groups	1+PRN	3+PRN	*P*
No. of eyes	35	32	-
BCVA (logMAR)			
Baseline	0.67±0.48	0.71±0.56	0.274
3mo	0.34±0.19	0.36±0.20	0.735
6mo	0.32±0.35	0.33±0.23	0.923
12mo	0.31±0.26	0.33±0.17	0.946
CMT (μm)			
Baseline	346.49±65.99	360.10±82.31	0.834
3mo	280.17±54.36	292.63±75.20	0.828
6mo	264.37±46.41	253.74±57.42	0.815
12mo	257.29±40.47	251.97±48.26	0.891
Total intravitreal injections	2.51±0.98	3.74±1.22	0.012
No. of eyes requiring additional injections	21 (60%)	6 (18.75%)	0.001

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; PRN: *Pro re nata*.

Choroidal Neovascularization Recurrence and Retreatment A total of 21 (60%) and 6 (18.75%) eyes with CNV recurrence in groups A and B, respectively, needed to be treated again (χ^2=11.832; P<0.05). The average number of injections in group A was 2.51±0.98, whereas that in group B was 3.74±1.22. The difference between the two groups was statistically significant (-2.813; P<0.05).

Complications After Treatment Eight patients (11.94%) had subconjunctival bleeding after intravitreal injection. The bleeding was absorbed within 1wk after operation without treatment. The IOP was increased in five patients (7.46%) within 2h after the operation and returned to normal within 24h without treatment. During the follow-up, no systemic adverse reactions, such as cataracts, glaucoma, vitreous haemorrhage, RD, intraocular infection, uveitis and cardiovascular or cerebrovascular diseases, were observed.

DISCUSSION

PM is estimated to affect up to 3% of the global population and is a particularly frequent cause of vision impairment and blindness in the young working-age population, particularly in Asian countries[7]. Therefore, PM is associated with a considerable social and economic burden. CNV secondary to PM is the main factor leading to the decline in vision[15]. A radiation study observed the long-term clinical efficacy of ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) (0.5 mg) and verteporfin PDT for the treatment of PM-CNV and reported that ranibizumab was superior to verteporfin in terms of improving vision and diminishing neovascularization 12mo after treatment[16]. Anti-VEGF therapy has replaced PDT as the first-line treatment of PM-CNV[17]. It can prevent the growth of neovascularization, reduce the exudation of immature neovascularization and significantly improve vision. At present, ranibizumab, aflibercept, and conbercept are the commonly used anti-VEGF drugs in China. Conbercept is an anti-VEGF drug independently developed in China. It is a recombinant fusion protein with a high affinity for VEGF. It can bind to VEGF closely and block all subtypes of VEGF-A, VEGF-B, and PlGF at the same time. In April 2014, conbercept was officially approved by the CFDA. It was first used to treat wet age-related macular degeneration and demonstrated a good curative effect[8]. Currently, the indications of intravitreal injection with conbercept include age-related macular degeneration, CNV secondary to PM or other causes.

In 2016, Zeng *et al*[18] retrospectively analysed 37 patients (37 eyes) with PM-CNV and reported the application of conbercept for the first time. A significant increase in the BCVA, a significant decrease in CMT, decreased (or no) leakage of fluorescein in FFA, and no local and systemic adverse reactions were observed during treatment and the one-year follow-up period. In recent years, scholars in China and other countries have conducted several clinical studies on the intravitreal injection of conbercept for the treatment of PM-CNV[15,19]. Yan *et al*[20] retrospectively analysed 42 eyes of PM-CNV patients who received intravitreal injections of 0.5 mg/0.05 mL of conbercept once monthly for the first 3mo, followed by an additional injection based on monthly visits. Compared with the baseline, the visual acuity of the patients was significantly improved at 3mo after the first treatment and continued to improve or stabilise at 12mo. The central retinal thickness and lesion area decreased mostly in the first 3mo, and this maintained up to the end of follow-up. The mean number of injections was 3.76.

Currently, the anti-VEGF treatment schemes commonly used for the treatment of PM-CNV include 1+PRN and 3+PRN, both of which have been proven to be effective, but the selection criteria for the two schemes remain inconclusive[21]. Nie *et al*[22] retrospectively analysed that 34 pathologic myopic patients with CNV were treated with intravitreal conbercept

0.5 mg with a follow up of 12mo. The study used 1+PRN regimen as the primary treatment for mCNV. The BCVA of all patients demonstrated improved or stable for up to 12mo. The CNV size and CMT decreased significantly in 2mo and then remained stable until the end of the follow-up period. However, 88.23% of patients need more injections due to mCNV recurrence. Wasiluk *et al*[23] reported 17 patients (17 eyes) with myopic CNV treated with intravitreal ranibizumab (3+PRN regimen) with at least 30-month follow-up. The 47% of patients did not require a re-injection till the end of the follow-up period. The results of many studies indicated that there is no significant difference between the two treatment schemes in terms of improved vision[24]. However, some scholars believe that the 3+PRN regimen can make the initial treatment reach the loading dose, which may reduce the recurrence rate or delay the CNV recurrence[25]. Likewise, the results of the current study revealed no significant difference in BCVA between the 1+PRN and 3+PRN groups after 12mo of follow-up. The recurrence rate of CNV in the 3+PRN group was lower than that in the 1+PRN group; however, 1+PRN group needed more treatment during the end of the follow-up period. Kung *et al*[21] reported the clinical efficacy of ranibizumab for the treatment of PM-CNV over a period of 12mo. After 12mo of follow-up, 17 out of 25 eyes in the 1+PRN group and 5 out of 21 eyes in the 3+PRN group needed reinjection. The total number of injections in the 3+PRN group (3.57±1.12) was significantly higher than that in the 1+PRN group (2.32±1.22; P=0.001). The results indicated no significant difference in vision improvement between the two groups. The 3+PRN group needed more injections but were less likely to need retreatment.

Ranibizumab is a monoclonal antibody fragment that can closely bind to VEGF-A and block its stimulation of VEGFR1 and VEGFR2 receptors[26]. Conbercept is a recombinant fusion protein with more binding targets and can closely bind with VEGF-A, VEGF-B, and PlGF. Chen *et al*[27] compared the clinical efficacies of intravitreal injections of conbercept and ranibizumab for the treatment of PM-CNV over a two-year period; the patients in the two groups were treated with 1+PRN. Within 2y, the average number of injections in the conbercept group was 3.94±1.88, whereas that in the ranibizumab group was 4.06±1.82. After 24mo of follow-up, the logMAR BCVA values in the two groups were significantly higher than those before treatment. There was no significant difference in the logMAR BCVA between the two groups at baseline and 1, 3, 6, and 12mo after the treatment. The logMAR BCVA in the conbercept group significantly increased at 1mo after treatment, but no significant improvement was observed from 1 to 3mo post-treatment. The logMAR BCVA in the ranibizumab group increased by varying degrees at 1, 2, and 3mo after treatment. No significant differences in visual acuity and macular anatomy were observed between the two anti-VEGF drugs.

Aflibercept (Eylea; Regeneron, Inc., Tarrytown, NJ, USA) and conbercept (Langmu; Kanghong, Inc., Sichuan, China) belong to the fusion protein anti-VEGF group of drugs and have a strong affinity for VEGF-A, VEGF-B, and PlGF[28]. In the MYRROR trial[29], an international, phase III, multi-centre, randomised, double-blind and sham-controlled study, 122 patients with PM-CNV were randomly divided into the treatment group (91 cases) and sham treatment group (31 cases). The treatment group received the 1+PRN regimen with the first intravitreal injection of aflibercept (2 mg). After 24wk of treatment, the BCVA was found to increase by 12.1 letters in the treatment group and decrease by two letters in the sham treatment group (P<0.0001). The patients in the sham treatment group were treated with aflibercept from week 24. However, the BCVA of these patients was increased by only 3.9 letters at the 12th month of follow-up. The BCVA in the treatment and sham treatment groups were increased by 13.5 and 3.9 letters, respectively (P<0.0001), after 48wk of follow-up. These data indicate that Aflibercept was effective for the treatment of PM-CNV and could significantly improve the vision; however, it should be used on time to maximise the benefits of the drug.

The safety of intravitreal anti-VEGF agents was also reported in many studies[30-33]. The RADIANCE, BRILLIANCE and LUMINOUS studies evaluated the use of ranibizumab for mCNV. In the RADIANCE study, most of the ocular adverse events (AEs) were minor AEs such as conjunctival hemorrhage and punctate keratitis. This study also reported two cases of ocular serious AEs (SAEs), one (0.9%) case of corneal erosion and one (0.8%) case of retinoschisis[16]. Similar to RADIANCE, the most frequently reported ocular AE was minor AE of conjunctival hemorrhage in the BRILLIANCE study[34]; however, there were two cases of RD and one case of endophthalmitis. In the LUMINOUS study[35], the most common ocular AEs were increased IOP (1.9%), one case of retinal detachment and one case of subretinal fibrosis. In the phase III PHOENIX study[36], conbercept was well tolerated with no systemic AEs or SAEs. The most common ocular AEs were associated with intravitreal injections, such as conjunctival hemorrhage, and increased IOP. In recently, a case of macular hole formation and RD after intravitreal conbercept injection for the treatment of CNV secondary to degenerative myopia has been reported[37].

Intravitreal injection is an invasive treatment. The risk of RD and intraocular infection after multiple injections is high in patients with PM, which could lead to an increase in the treatment costs for the patients. When selecting the treatment

plan, it is important to comprehensively consider the condition of the eye and the economic status of the patient.

In the present study, the patients were divided into two groups based on the treatment scheme. Intravitreal injection of conbercept was used to treat PM-CNV. After 12mo of follow-up, the BCVA of the patients in the two groups increased to varying degrees, the CMT significantly decreased, and the curative effects of the two treatment schemes were found to be significant. During the treatment and follow-up, no serious ocular and systemic complications were reported in any of the patients, indicating the safety and efficacy of conbercept for the treatment of PM-CNV.

This study has some limitations. The sample size was small, the correlation analysis between the curative effect and onset time was not evaluated, and the follow-up time was not sufficiently long. Additional long-term prospective and randomised trials using an increased number of samples are warranted to compare the safety and efficacy of these two different dosing regimens.

In conclusion, this study demonstrated that the intravitreal injection of conbercept using the 1+PRN and 3+PRN treatment schemes can improve the visual acuity of PM-CNV patients, reduce macular oedema and reduce the level of CMT. The 3+PRN regimen had a lower recurrence rate of PM-CNV when compared with the 1+PRN regimen but required a longer treatment time. Nonetheless, the two schemes of intravitreal injection of conbercept appear to have a safe and long-term effect in patients with PM-CNV.

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