

# Outcomes of Conbercept therapy for choroidal neovascularization secondary to pathological myopia

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## 康柏西普治疗病理性近视脉络膜新生血管的疗效观察

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### 摘要

**目的:**通过光学相干断层扫描血流成像术(OCTA)观察玻璃体腔注射康柏西普治疗病理性近视脉络膜新生血管(pm-CNV)的疗效。

**方法:**回顾性分析23位患者26眼接受康柏西普治疗pm-CNV 1y的治疗效果。首诊中,所有患者通过荧光素眼底血管造影(FFA)和OCTA确诊为pm-CNV。所有患者均接受“1+PRN”的治疗方案。随访中,记录患者的最佳矫

正视力(BCVA),OCTA测量中心凹厚度(CFT)和CNV面积。

**结果:**1a后,平均BCVA(LogMAR)从基线视力 $0.66\pm 0.51$ 提升到 $0.39\pm 0.38$ ( $t=3.528, P=0.004$ )。CFT在治疗前为( $275.08\pm 48.74$ ) $\mu\text{m}$ ,治疗后1a,CFT为( $205.15\pm 43.74$ ) $\mu\text{m}$ ( $t=4.630, P=0.001$ )。CNV面积在治疗前的基线为( $0.48\pm 0.24$ ) $\text{mm}^2$ ,治疗后1a的面积为( $0.15\pm 0.11$ ) $\text{mm}^2$ ,具有明显的统计学差异( $t=5.329, P=0.000$ )。有21眼行1次注射,4眼行2次注射,仅有1眼行3次注射。在治疗过程中,没有严重不良事件发生。

**结论:**应用“1+PRN”方案行玻璃体腔注射康柏西普可以提高pm-CNV患者视力,OCTA可以观察到CFT减轻和CNV面积的减小,但是长期的随访仍然要观察。

**关键词:**病理性近视脉络膜新生血管;康柏西普;光学相干断层扫描血流成像术;疗效

### Abstract

• **AIM:** To evaluate the one-year outcome of intravitreal conbercept injections for the treatment of choroidal neovascularization secondary to pathological myopia (pm-CNV) by optical coherence tomography angiography (OCTA).

• **METHODS:** The medical records of 26 consecutive eyes of 23 patients who received intravitreal injections of conbercept for pm-CNV with a follow-up of 1y were retrospectively reviewed. All the patients were diagnosed by fundus fluorescein angiography (FFA) and OCTA at the first visit. All approaches were performed as “1+PRN” treatment. Outcomes included best-corrected visual acuity (BCVA), central foveal thickness (CFT) and the mean CNV area by OCTA.

• **RESULTS:** Mean BCVA improved from ( $0.66\pm 0.51$ ) at baseline to ( $0.39\pm 0.38$ ) at 1y ( $t=3.528, P=0.004$ ). The CFT before treatment and after 1y after were ( $275.08\pm 48.74$ ) $\mu\text{m}$  and ( $205.15\pm 43.74$ ) $\mu\text{m}$  respectively ( $t=4.630, P=0.001$ ). The mean pm-CNV areas before treatment and after 1y treatment were ( $0.48\pm 0.24$ ) $\text{mm}^2$  and ( $0.15\pm 0.11$ ) $\text{mm}^2$  respectively, with a significant difference among them ( $t=5.329, P=0.000$ ). Twenty-one eyes had no needs after the first treatment. Four eyes received 2 injections and only one eye received 3 injections. No severe adverse events were noted relevant to the therapy.

• **CONCLUSION:** Intravitreal conbercept can improve the vision and relieve CFT and CNV area for the treatment of pm-CNV with “1+PRN” by OCTA for 1y, however, long-term follow-up still need to be performed.

• **KEYWORDS:** choroidal neovascularization secondary to pathological myopia; Conbercept; optical coherence tomography angiography; curative effect  
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## INTRODUCTION

Myopia is a global public health issue. It is estimated that 28.5% of men and 27.3% of women are myopia in the world<sup>[1]</sup>. In Asia, the situation is even worse. There are nearly 400 million myopic patients in China alone, and the prevalence of myopia in adolescents is as high as 90%<sup>[2]</sup>. A previous study stated that the population with myopia will be approximately 5 billion in 2050<sup>[3]</sup>.

Myopic choroidal neovascularization (CNV) is a common cause of vision loss in patients with pathological myopia<sup>[4]</sup>. Myopic CNV is more common in young people, whose chorioretinal complexes is thinner and more likely to be Asian<sup>[5]</sup>. Myopic CNV brings heavy burdens to families and society. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is the “gold standard treatment” for myopic CNV<sup>[6]</sup>. Intravitreal anti-VEGF brings new and effective treatment ways to treat myopic CNV<sup>[7]</sup>. There are 3 clinically available anti-VEGF agents in western countries, including ranibizumab (Lucentis™; Genentech, Inc., South San Francisco, CA, USA, and Novartis Pharma AG, Basel, Switzerland), aflibercept (VEGF-Trap Eye, Eylea™; Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) and bevacizumab (Avastin™; Genentech, San Francisco, CA, USA). Conbercept (KH902; Chengdu Kanghong Biotech Co. Ltd., Sichuan, China) is a new recombinant fusion protein, and it consists of the extracellular domain 2 of VEGF receptor 1 and extracellular domains 3 and 4 of VEGF receptor 2 fused to the Fc portion of human immunoglobulin G1, which has high affinity for all VEGF isoforms and placental growth factors (PIGF)<sup>[8]</sup>. Both intravitreal ranibizumab and intravitreal bevacizumab can significantly improve best-corrected visual acuity (BCVA) of eyes with myopia CNV<sup>[9]</sup>. Two large, multi-center, double-masked, randomized, controlled clinical trials, *i. e.* the RADIANCE (Ranibizumab and PDT evaluation in myopic choroidal neovascularization) study and the MYRROR (Intravitreal aflibercept injection in patients with myopic choroidal neovascularization) study, have reported beneficial effects of treatment<sup>[10-11]</sup>. The optical coherence tomography angiography (OCTA) seems to be a high sensitive way for the detection of myopic CNV<sup>[12]</sup>, and to monitor vascular changes after anti-VEGF treatment<sup>[13]</sup>. In this study, we attempted to evaluate the one-year outcomes of patients with CNV

secondary to pathologic myopia by treating with intravitreal conbercept by OCTA.

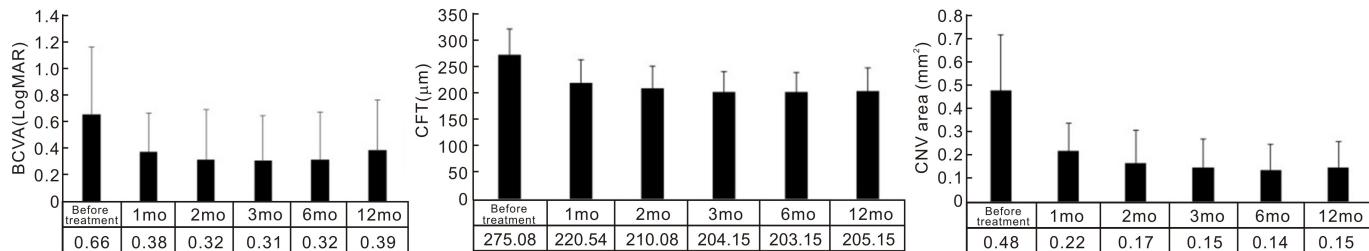
## SUBJECTS AND METHODS

We retrospectively reviewed 26 eyes consecutive medical records with CNV secondary to pathologic myopia which were treated with intravitreal conbercept and were followed for one year in 23 patients. This study was approved by the hospital's institutional review board. All approaches were known as “1+pro re nata (1+PRN)” treatment regimens, namely, one intravitreal injection of conbercept at the baseline followed by as-needed reinjection. All patients were informed of the possible adverse effects. All the myopic CNV were diagnosed by fundus fluorescein angiography (FFA) and OCTA. The inclusion criteria were as follows: high myopia with a spherical equivalent of -8.00 diopters or more and an axial length of at least 26.0 mm, active subfoveal CNV, treatment only with intravitreal conbercept and follow-up of at least 12mo. Exclusion criteria were as follows: CNV secondary to causes other than myopic CNV (including age-related macular degeneration (AMD), angioid streaks, choroiditis, or trauma), any chorioretinopathy other than pathologic myopia (including central serous chorioretinopathy, diabetic retinopathy, retinal vein occlusion, vasculitis, or uveitis), other coexisting conditions associated with myopia needing surgical treatments (*i. e.* macular hole and retinal detachment).

The first treatment for each eye was performed between Jan. 2018 and July 2018. At baseline, each eye underwent a comprehensive ophthalmologic examination that included as follows: slit-lamp biomicroscopy, measurement of BCVA and intraocular pressure (IOP), dilated fundus examination, FFA, and OCTA. FFA was used to evaluate the location, composition, and activity of the CNV lesion, whereas OCTA was used to confirm the presence of CNV and measure central foveal thickness. All of the results were checked by the same doctor.

To prevent infection, levofloxacin eye drops were used 2d before treatment four times 1d. After obtaining written consent, we performed the procedures with surface anesthesia. All the eyes received intravitreal injections of conbercept (0.05 mL/0.5 mg) under sterile conditions initially through the pars plana using a 30-gauge needle. And additional injections of conbercept which were administered as needed were determined based on OCTA findings.

We followed all eyes 1d after the injection (s) to determine if there were complications and then 1mo, 2mo, 3mo, 6mo and 12mo. The patients were informed to review if there were any loss of vision. At each follow-up, every patient underwent examinations, including measurements of BCVA and IOP, slit-lamp biomicroscopy, dilated fundus examination, and OCTA. FFA was performed as required. We recorded the patient demographics and the results of examinations at baseline and each visit. The outcomes of the study included



**Figure 1** The changes before treatment and follow-up by conbercept.

**Table 1** Characteristics of the study

Parameters	Patients (n=23)
Race (Chinese)	
Eyes (single/both)	26 (23/3)
Age, y	45.84±13.78
Sex (female/male)	16/7
Refractive error, D	-12.64±3.54
Axial length (mm)	27.56±3.11

BCVA, CFT, CNV areas and the total number of injections. BCVA was measured using Snellen charts, and the measurements were converted into the logarithm of the minimum angle of resolution (LogMAR) for data analysis. We used SPSS statistics 17.0 software for statistical analysis. A paired samples test *P* value of < 0.05 was regarded as statistically significant.

**RESULTS**

All patients were Chinese. Twenty-six eyes of 23 patients (16 female and 7 male, mean ages at baseline 45.84±13.78 years old, range 23–65) were included in the analysis. The mean spherical equivalent refractive error was -12.64±3.54 diopters (range -8.50 to -20.00). The mean axial length of 27.56±3.11 (range: 26.55–31.33) mm (Table 1).

The mean BCVA at baseline was 0.66±0.51. It improved significantly to 0.38±0.29 at 1mo (*t* = 5.347, *P* = 0.000), 0.32±0.38 at 2mo (*t* = 4.961, *P* = 0.000), 0.31±0.34 at 3mo (*t* = 4.175, *P* = 0.001), 0.32±0.36 at 6mo (*t* = 4.131, *P* = 0.001), 0.39±0.38 at 1y (*t* = 3.528, *P* = 0.004). The CFT at baseline was 275.08±48.74 μm. It decreased significantly to 220.54±45.06 μm at 1mo (*t* = 7.622, *P* = 0.000), 210.08±43.14 μm at 2mo (*t* = 8.364, *P* = 0.000), 204.15±38.71 μm at 3mo (*t* = 7.393, *P* = 0.000), 203.15±37.52 μm at 6mo (*t* = 7.773, *P* = 0.000), 205.15±43.74 μm at 1y (*t* = 4.630, *P* = 0.001). The pm-CNV area at baseline was (0.48±0.24) mm<sup>2</sup>, it decreased significantly to (0.22±0.12) mm<sup>2</sup> at 1mo (*t* = 4.141, *P* = 0.001), (0.17±0.14) mm<sup>2</sup> at 2mo (*t* = 5.814, *P* = 0.000), (0.15±0.12) mm<sup>2</sup> at 3mo (*t* = 4.557, *P* = 0.001), (0.14±0.11) mm<sup>2</sup> at 6mo (*t* = 5.173, *P* = 0.000), (0.15±0.11) mm<sup>2</sup> at 12mo (*t* = 5.329, *P* = 0.000) (Figure 1).

Our retrospective study included 26 eyes with active pm-CNV treated with at least 1 injection of conbercept. Twenty-one eyes had no need after the first treatment. Four eyes received 2 injections and only one eye received 3 injections. Similar to

other anti-VEGF drugs, only conjunctival haemorrhage caused by the intravitreal injections procedure were observed. After about 15d conjunctival haemorrhage gradually absorbed without treatment.

**DISCUSSION**

VEGF, an angiogenic and vasopermeability factor, has been implicated in the pathogenesis of CNV, and myopic CNV lesions are associated with increased levels of VEGF<sup>[14-15]</sup>. Raised levels of VEGF may induce proliferation of choroidal vascular endothelial cells, resulting in the development of CNV<sup>[16]</sup>. Researchers have shown that anti-VEGF drugs are effective in reducing retinal thickness and improving visual acuity<sup>[17]</sup>. Anti-VEGF drugs have been developed to reduce the angiogenic activity of upregulated VEGF, which is detected in eyes with CNV<sup>[7]</sup>. Owing to its affordability and its efficiency in controlling CNV leakage, conbercept is widely used to treat fresh mCNV<sup>[18]</sup>. Conbercept is approved to treat neovascularization age-related macular degeneration, diabetic macular edema and myopic CNV by the China State Food and Drug Administration since January 1, 2020. It has not been marketed in other countries. The preclinical studies have shown that conbercept has a longer half-life and a stronger binding affinity to VEGF-A and it has advantages over ranibizumab and bevacizumab<sup>[19]</sup>.

OCTA is a novel, noninvasive imaging technique that allows visualization of the retinal microvasculature. The OCTA can be a valuable tool in detecting myopic CNV<sup>[12]</sup>. Compared with FFA and structural SD-OCT B-scan, OCTA does not provide information on leakage of the dye<sup>[20]</sup>. So, in our study, all the myopic CNV eyes were diagnosed by FFA and OCTA at the first visit. CFT and CNV area were observed with OCTA in the follow-up. Study of OCTA showed a statistically significant reduction of the CNV area after anti-VEGF treatment<sup>[13]</sup>. In our study, the myopic CNV area also significant reduced at 12mo follow-up by treating with conbercept.

Sun *et al*<sup>[21]</sup> reported a case of macular hole formation and retinal detachment after intravitreal conbercept injection for the treatment of CNV secondary to degenerative myopia. In our study, no complications were caused by conbercept itself, only conjunctival haemorrhage was caused by intravitreal injections, and about 15d later, conjunctival haemorrhage was gradually absorbed.

Yan *et al*<sup>[22]</sup> reported that intravitreal conbercept with “3 + PRN” for treating myopic CNV was an effective treatment.

71.4% of eyes gained a BCVA improvement of at least 3-line, and the central retinal thickness decreased in the one year followed up. Moreover, for the study of conbercept, only the visual acuity and CFT were examined, but the area of CNV was not examined. In our study, we measure the area of CNV, so that the CNV can be better assessed. The SMILE study suggests that eyes treated with “1+PRN” ranibizumab for myopic CNV do just as good as those treated with a 3-monthly in function and anatomy over 12mo<sup>[9]</sup>.

In our study, twenty-one eyes had no needs after the first treatment. Four eyes received 2 injections and only one eye received 3 injections with the “1+PRN” treatment regimens. The results show that most of the pm-CNV patients can improve their vision after one treatment by intravitreal conbercept. Recurrence of CNV is usually observed within the first year after onset<sup>[10]</sup>. We've only been studied for a year, and we need to continue to observe if there are recurrences.

In conclusion, all results in our study indicated that intravitreal conbercept with “1+PRN” treatment protocol may be an effective and safe in resolving pm-CNV over a period of one year by OCTA. In addition, in the first visit, FFA and OCTA are used for diagnosis. In the follow-ups, the examinations by OCTA can save time and cost for patients. Nevertheless, potential limitations should be mentioned in the present study. First, the small sample size, only 12mo follow-up periods and retrospectively designed study are the drawbacks. The prospective study with large number of subjects and long term follow-up is required in the future. Second, different age groups may have different sensitivity to conbercept, so age group analysis is needed. Third, the present studies are only for Chinese, other human races are needed for conbercept in the future.

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