• Clinical Research •

Efficacy of conbercept after switching from bevacizumab/ranibizumab in eyes of macular edema secondary to central retinal vein occlusion

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Abstract

● **AIM:** To explore the efficacy of conbercept after switching from bevacizumab/ranibizumab in eyes of central retinal vein occlusion (CRVO) through optical coherence tomography angiography (OCTA).

● **METHODS:** Patients with prior treatment of a minimum of three consecutive intravitreal injections of either bevacizumab or ranibizumab, followed by injection of conbercept, were recruited. The minimal follow-up period after switching was 12mo. Central retinal thickness (CRT), best-corrected visual acuity (BCVA), the interval of injections was reviewed. Perfusion density (PD) and vascular length density (VLD) of superficial and deep capillary plexus were acquired from OCTA images before and after switching.

● **RESULTS:** Twenty-four eyes were included. CRT significantly decreased from 460.71±153.23 μm (before switching) to 283.92±38.27 μm at the end of follow-up (P<0.001). However, BCVA gained to some extent (from 0.98±0.33 to 0.76±0.42 logMAR) but the difference was not significant (P=0.070). After switching to conbercept the injection interval extended from 5.2±2.3wk to 8.3±3.9wk (P=0.012). At the end of follow-up, PD of deep retinal layer decreased significantly compared with before switching (from 34.62%±5.27% to 33.26%±5.82%, P=0.016), similar result was found in VLD of deep retinal layer but not in PD or VLD in superficial layer.

● **CONCLUSION:** In cases of refractory macular edema secondary to CRVO, switching to conbercept improves macular thickness and extends interval of injection. Retinal microvasculature cannot improve with treatment of conbercept.

● **KEYWORDS:** conbercept; central retinal vein occlusion; switching

INTRODUCTION

Macular edema (ME) secondary to central retinal vein occlusion (CRVO) is a common cause of vision loss[1]. Vascular endothelial growth factor (VEGF) has been demonstrated to play an important role in the hypoxia course after the occlusion of the retinal vein[2-4]. Numerous studies have proved that anti-VEGF agents, including bevacizumab, ranibizumab, and aflibercept, are basically safe and effective[5-7]. Similar to aflibercept, conbercept (Lumitin; Chengdu Kang Hong Biotech Co., Ltd., Sichuan Province, China) is a fusion protein composed of the extracellular domain 2 of VEGF receptor 1 and extracellular domains 3 and 4 of VEGF receptor 2 combined with the Fc portion of the human immunoglobulin G1[8]. Prior studies indicated that conbercept showed favorable safety and efficacy in the treatment of ME secondary to retinal vein occlusion[9-10]. In real clinical practice, some cases trend to respond insufficiently to anti-VEGF injections or to rebound repeatedly. Although switching strategy is very common[11-12], little attention has been paid to the switching to conbercept.

Optical coherence tomography angiography (OCTA) is a new, noninvasive technology that provides detailed information about the retinal microvasculature with the measurements of vessel density and foveal avascular zone[13]. The evaluation of macular perfusion makes it possible to know more about the change after intravitreal injection of anti-VEGF agents. In this study, we quantified retinal vessel density of both superficial and deep layer of retina to evaluate the change of retinal vasculature and macular thickness after switching from bevacizumab and/or ranibizumab to conbercept.

SUBJECTS AND METHODS

Ethical Approval This was a retrospective study that was approved by China-Japan Friendship Hospital Ethics

Committee and adhered to the Declarations of Helsinki. Informed consent was obtained from all patients who were enrolled in the study.

Subject Recruitment From March 2016 to December 2018, medical records of cases of ME due to CRVO were retrospectively reviewed.

Including criteria: 1) Patients aged 18 years or older with diagnosed CRVO and confirmed ME through optical coherence tomography (OCT) scan; 2) Prior treatment with a minimum of three consecutive intravitreal injections of either bevacizumab (1.25 mg/0.05 mL) or ranibizumab (0.5 mg/0.05 mL); 3) Switching to conbercept (0.5 mg/0.05 mL) due to refractory ME, which was defined as persistent ME or recurrent ME that initially resolved after treatment with bevacizumab and/or ranibizumab but did not respond to following repeated injections; 4) Following conbercept injection using a *pro re nata* (PRN) regimen; 5) With a follow-up period of at least 12mo after switching; 6) OCTA was performed before switching and in the twelfth month after switching.

Excluding criteria: 1) Eyes of primary or neovascular glaucoma and initial intraocular pressure (IOP) exceeded 21 mm Hg; 2) Vitrectomized eyes; 3) The presence of active confounding retinal or ocular disease (*e.g.*, severe diabetic retinopathy, exudative macular degeneration, macular hole, *etc*).

Demographic information, best-corrected visual acuity (BCVA, converted to logMAR), IOP, central retinal thickness (CRT), the interval between injections and the number of injections were reviewed and collected.

OCTA Imaging and Assessment All recruited subjects underwent OCTA scan with a swept-source OCT (Triton DRI-OCT, Topcon, Inc., Tokyo, Japan). Raster-pattern retinal scans were obtained through the macula using scanning patterns of 6×6 mm^2 in all patients. Images with a quality score below 40 were excluded. We also excluded low-quality images with obvious motion artifacts, signal loss. The built-in software (IMAGEnet6, v1.23.15008, Basic License 10) was used to identify superficial capillary plexus (SCP) and deep capillary plexus (DCP). The SCP was set at 2.6 μm below the internal limiting membrane, and the outer boundary at 15.6 μm below the junction between inner plexiform and inner nuclear layer (IPL/INL). The DCP started at 15.6 μm below IPL/INL, with the outer boundary at 70.2 μm below IPL/INL. Automated segmentation of macular thickness was manually corrected. Images which were difficult to segment were also excluded.

Images of SCP and DCP were exported and analyzed with Image J software (1.8.0_112, http://imagej.nih.gov/ij/; National Institutes of Health, Bethesda, Maryland, USA) to acquire perfusion density (PD) and vascular length density (VLD). We calculated the parafoveal vessel densities for the SCP and DCP. The parafoveal region was set to be an annulus centered on the fovea with inner and outer ring of diameters of 1 and 3 mm, respectively. PD was the percentage of pixels occupied by blood vessels in the binary image of the grayscale OCTA image. VLD was defined as the ratio of skeletonized vessel length to the total area. Images were imported to Image J and binarized to assign each pixel to be either "perfused" or "background". PD was calculated from the binarized images with a vascular density plugin application. After binarizing, a skeletonized slab was created, representing vessels one pixel in width, and VLD was calculated with "Analyze Skeleton" mode in Image J[14-15].

Table 1 Demographics *n* (%)

Parameters	Data
No. of patients (eyes)	24
Age (y), mean±SD	58.50±15.36
Female/male	11/13
Diabetes	8 (33.3)
Hypertension	11 (45.8)
History of cataract surgery	4 (16.7)
Ischemic CRVO	13 (54.2)

CRVO: Central retinal vein occlusion.

Statistical Analysis Statistical analysis was performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA). Mean values with 1 standard deviation are recorded when data is normally distributed. Paired samples *t*-tests were used to compare injections intervals and OCTA parameters before and after switching. One way analysis of variance and the LSD post hoc test were used to compared BCVA, CRT, and IOP. All tests were two-tailed, and the P value<0.05 was defined as statistically significant.

RESULTS

Clinical Demographics We initially included 29 eyes of 29 patients. Segmentation errors were found in all OCTA images and manual correction were used. But 5 of them were excluded due to low-quality images with obvious motion artifacts and signal loss which made even manual segmentation impossible. Finally, twenty-four eyes of 24 patients were included in the study. Eleven (45.8%) were male and 13 (54.2%) were female. The mean age was 58.50±15.36 years old (ranging from 24 to 71). Eight of the patients were diagnosed as diabetes and two of them had mild non-proliferative diabetic retinopathy. Eleven of the patients had hypertension. Four eyes had a history of cataract extraction and intraocular lens implantation and the other 20 eyes were phakic. Thirteen of the included eyes were ischemic CRVO and had received laser treatment. None of the fellow eyes were diagnosed as CRVO or ME (Table 1).

Previous Treatment Six eyes (25%) received only ranibizumab (9-15 injections) previously while 15 eyes (62.5%) received only bevacizumab (8-20 injections) and 3 eyes (12.5%) received injections of both, two of which were switched

from bevacizumab to ranibizumab (5 and 3 injections for one subject; 4 and 4 injections for another) and one of which was switched inversely (6 and 4 injections). The number of injections ranged from 8 to 20. The mean number of injections was 14.3±5.7 within a mean follow-up duration of 16.1mo (12-29mo) and the mean interval between injections was 5.2±2.3wk.

Change of Injections After switching to conbercept, the mean follow-up duration was 13.8 (12-16)mo. The number of injections decreased to 8.1±5.5 (4-10), which was statistically significant (P=0.008) compared with before switching. The mean injection interval increased to 8.3±3.9wk correspondingly (P=0.012).

Change of BCVA and CRT The mean BCVA (logMAR) at baseline was 1.06±0.48 and before switching to conbercept 0.98±0.33 (no significantly improved compared to baseline, P=0.469). It changed to 0.72±0.35 in one month after the first injection of conbercept (P=0.005 compared with baseline, P=0.032 compared with before switching) and 0.76±0.42 at the end of follow-up (P=0.012 compared with baseline, P=0.070 compared with before switching, and P=0.733 compared with one month after switching; Figure 1). The average of CRT at baseline was 559.67±175.71 μm, before switching 460.71±153.23 μm (P=0.005 compared with baseline), 1mo after switching 296.21±47.55 μm (P<0.001 compared with baseline and P<0.001 compared with before switching) and at the end of follow-up 283.92±38.27 (P<0.001 compared with baseline, P<0.001 compared with before switching, P=0.725 compared with 1mo after switching; Figure 2). The IOPs at four visits were 14.85±3.89, 13.77±3.51, 14.16±4.04, and 14.52±3.78 mm Hg, with no significant differences (P=0.704).

Change of OCTA Parameters At the end of follow-up, PD of DCP decreased significantly to 33.26%±5.82% (P=0.016) compared with before switching (34.62%±5.27%) and a significant decrease of VLD of DCP was also found (from 25.10±3.60 to 24.41±3.35 mm^{-1}, P=0.040). No significant change of VLD of SCP was observed at the last follow-up (16.75±1.72 mm^{-1}) compared with before switching (16.94±2.01 mm^{-1}, P=0.667). Similar result was found in PD of SCP (from 32.52%±4.34% to 32.32%±3.46%, P=0.846; Figure 3).

Other Findings Over the follow-up period, no progression of diabetic retinopathy was observed in the two patients of mild non-proliferative diabetic retinopathy. Progression of posterior subcapsular cataract was found in one eye of the 20 phakic eyes during the follow-up after switching; the fellow eye had the similar progression of cataract and both eyes underwent cataract extraction and lens implantation.

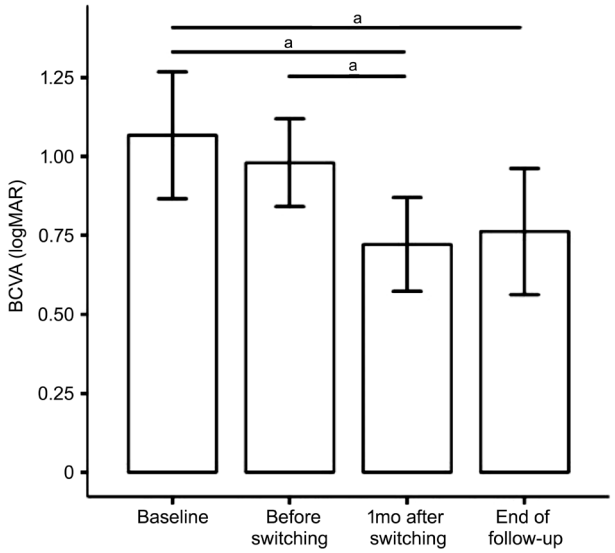

Figure 1 Change of BCVA at four time points After switching, BCVA gained significantly compared with before switching and baseline. At the end of follow-up, BCVA did not significantly improved compared with before switching. [a]P<0.05.

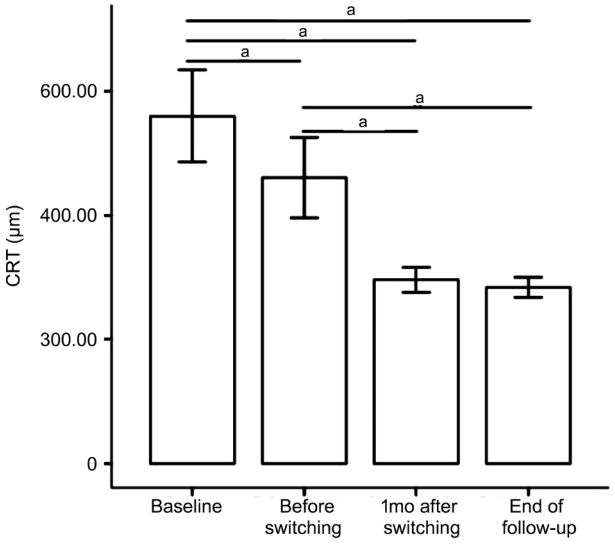

Figure 2 Change of CRT at four time points After switching, CRT decreased significantly compared with before switching and baseline. At the end of follow-up, CRT maintained lower than baseline and before switching with significant difference. [a]P<0.05.

DISCUSSION

Anti-VEGF therapy has become the most commonly used treatment for ME secondary to CRVO. Numerous studies focused on the comparison about the efficacy of the anti-VEGF drugs[4]. A randomized clinical trial indicated 1) that the vision gain after treatment of ME due to CRVO was no worse using aflibercept compared with ranibizumab; 2) bevacizumab might be not noninferior to aflibercept; 3) aflibercept group had fewer injections[5]. Similarly, prior studies indicated that conbercept had the statistically same visual gains and safety as ranibizumab and had advantages over ranibizumab in terms of the number of injections for treating ME secondary to retinal vein occlusion[16-17]. Based on the advantage of fusion proteins over antibodies, aflibercept was chosen to treat refractory cases that either did not respond to ranibizumab/bevacizumab or

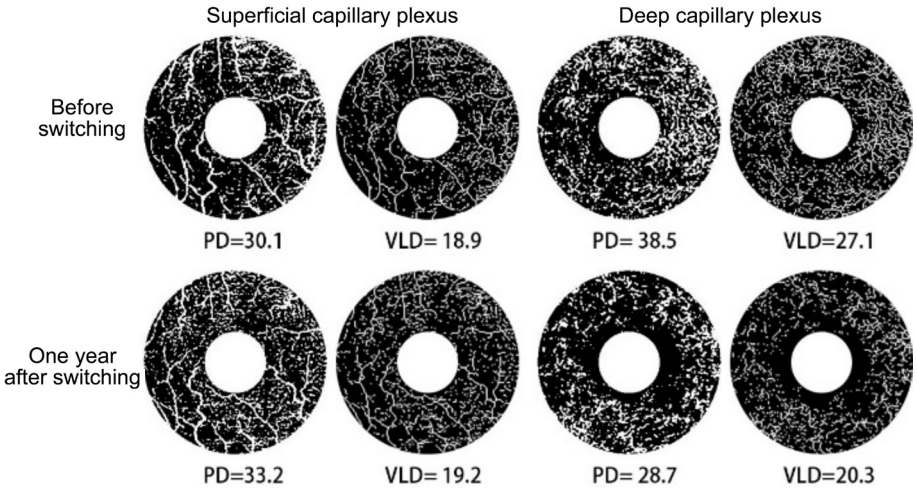

Figure 3 Example of the change in OCTA parameters after intravitreal injection of conbercept After switching the vessel density of SCP stays stable while the parameters of DCP decrease. PD: Perfusion density; VLD: Vascular length density.

rebounded frequently. Eadie *et al*[18] reported a six-eye case series of refractory CRVO responding favorably to aflibercept as a secondary therapy. Subsequently, several studies found that switching to aflibercept could stabilize vision, improve macular thickness and extend treatment intervals[19-22]. It was believed that the molecular characteristics of the higher affinity of aflibercept to VEGF-A might contribute to the superior treatment effect[23]. In addition, aflibercept bonded to not only VEGF-A but also VEGF-B and placental growth factor (PIGF)[24-25]. Besides, the tachyphylaxis after successive injection and the anti-bevacizumab/ranibizumab antibodies could serve as possible explanations of the previous recurrent ME[26].

As far as we know, this was the first study that evaluated the efficacy of switching to conbercept in refractory ME secondary to CRVO. In our study, significant improvement of CRT and BCVA was observed in the first month after switching to conbercept and the injection interval increased significantly in the follow-up period. The superior efficacy of conbercept comes from the high affinity to VEGF. As a fusion protein, conbercept also bonds to VEGF-A, VEGF-B and PIGF. Compared with aflibercept, conbercept contains one additional binding domain of VEGF receptor 2 which enhances the affinity[27-28]. Based on our findings and previous study, we believed conbercept could be a secondary therapy for refractory ME in CRVO eyes with prior treatment of bevacizumab and/or ranibizumab.

In our study, the BCVA improved significantly in the first month after switching compared with before switching, but the improved vision was not sustained until the end of follow-up although CRT maintained the same thickness. Impaired retinal microvasculature following the persistent or recurrent edema and might be the reason. In this study, we observed decreased vessel density in DCP in the end of follow period. Previous studies indicated that vessel density in both SCP and DCP decreased in eyes of CRVO compared with fellow eye and vessel density in DCP seemed to be impaired more significantly[29-31]. The deep retinal layer had more abundant microvasculature and might be more susceptible than the superficial layer in the pathogenesis of CRVO. Moreover, ME occurred mainly in deep layer. Recurrent or persistent ME may lead to drop-out of capillaries of DCP and this deterioration was hard to be reverted with anti-VEGF treatment[32]. Prior studies reported that anti-VEGF therapy could improve retinal ischemia in a short term, mainly manifested with improvement of vascular telangiectasia, dilation, and decreased non perfusion area[33-34]. Some recent studies showed unchanged or improved vessel density after treatment of conbercept with the follow-up period of 1 to 6mo[35-36]. Contradictorily, we observed decreased vessel density of DCP 12mo after use of conbercept. The variety could be result of different instruments, regions of interest, methods of calculating vessel density, and disease severity while the most likely reason may be different observation time. There exists the possibility that anti-VEGF therapy slows the progression of ischemia or even improves that within a short time but might not stop it in the long run. Our findings indicated that the ischemic damage of the deep retinal vessels may be progressive and nonreversible.

There were some limitations of this study, including the retrospective nature of the study and lack of control, and the small sample size, varied anti-VEGF agents before switching added the biases of the study and lowered the strength. Besides, since the analysis based on OCTA was performed only on the annulus area centered on the fovea, the findings of the study could not extend throughout the entire retinal vasculature. Further prospective controlled studies are warranted.

In conclusion, switching to conbercept in eyes of refractory ME secondary to CRVO extended injection interval and

improved macular anatomy while the vision improvement was not significant. Retinal microvasculature did not improve with treatment of conbercept.

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Conflicts of Interest: Zhao T, None; **Chen Y,** None; **Zhang HS,** None; **Chen Y,** None; **Wang ZJ,** None.

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