Optical coherence tomography angiography follow-up for long-term outcomes of conbercept treatment for myopic choroidal neovascularisation and idiopathic choroidal neovascularisation

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Research Article

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Abstract

Background: Optical coherence tomography angiography (OCTA) was performed as a follow-up to report 2-year outcomes of the use of two initial doses of intravitreal conbercept in subjects with myopic choroidal neovascularisation (mCNV) and idiopathic choroidal neovascularisation (iCNV).

Methods: 20 consecutive subjects with mCNV (group A) and 18 with iCNV (group B) were enrolled in this retrospective study. Subjects received 1.0 mg intravitreal conbercept at diagnosis and again 35 days later. Further injections of conbercept were needed when best-corrected visual acuity (BCVA) decreased; upon aggravation of metamorphosis, macular oedema, or haemorrhage; increased retinal thickness as documented by OCT; or leakage documented by OCTA.

Results: Group A comprised 8 men and 12 women (mean age, 31.72years). The mean follow-up duration was 24.95±1.03months (range: 23.5-27.2 months). Group B patients comprised 8 men and 10 women (mean age, 30.22 years). The mean follow-up duration was 25.67±1.35months (range: 24.5-29.5 months). Following intravitreal conbercept injection, vision improved in 17 group A subjects and 15 group B subjects. Vision remained stable in 3 group A and 3 group B subjects. The mean BCVA of group A improved from baseline logMAR 0.31±0.16 to logMAR 0.12±0.03 at the final follow-up(P=0.000); the mean BCVA of group B improved from baseline at logMAR0.33±0.16 to logMAR0.12±0.03 at the final follow-up(P=0.000). Metamorphopsia was reduced. The mean central retinal thickness at the last postoperative visits were reduced from pre-treatment levels of 311.83±30.95 in group A and 351.17±37.09 in group B to 229.56±5.75 and 227.67±4.98μm, respectively (P = 0.000 in group A and P = 0.000 in group B). The injections were well tolerated by all subjects, with no ocular or systemic complications.

Conclusion: OCTA used for mCNV and iCNV follow-up showed that intravitreal injection of 1 mg conbercept was effective in improving and stabilising vision as well as dramatically alleviating metamorphopsia.

Introduction

Eyes with a refractive error of more than − 6 diopters or an axial length of more than 26.5 mm and with typical pathologic changes at fundus are defined as having pathologic myopia (PM).[1] A recent systematic review has indicated that the prevalence of PM is 1–3% in adults, and that 5–11% of patients with PM develop CNV.[2] Several of the phenotypic features of PM are associated with increased risk of myopic choroidal neovascularisation (mCNV)—these include patchy atrophy, lacquer cracks,[3] thinning of the choroid and choriocapillaris,[4] and CNV in the other eye.[5] Choroidal neovascularisation (CNV) is the sight-threatening complication occurring in approximately 5.2–10.2% of highly myopic eyes.[6,7] CNV is one of the most common causes of irreversible central vision loss, deteriorates quality of life, and generates huge socioeconomic burdens. CNV secondary to PM has a very high incidence in Asian populations, and it mainly affects the population aged 40 and above.[8] The traditional therapeutic

modalities for CNV secondary to PM include thermal laser photocoagulation, surgical management, transpupillary thermotherapy, and photodynamic therapy with verteporfin. Verteporfin photodynamic therapy has been an established treatment for sub-foveal mCNV for many years; however, this treatment is not satisfactory in restoring visual acuity and is associated with long-term chorioretinal atrophy. In recent years, anti-vascular endothelial growth factor (anti-VEGF) agents in patients with mCNV have demonstrated substantial visual acuity gains, and the quality of life of patients undergoing anti-VEGF therapy has increased compared with photodynamic therapy.

The anti-VEGF agents have been proposed as the first-line therapy for sub-foveal and juxtafoveal CNV secondary to PM.[9] Administration of anti-VEGF biological agents, including ranibizumab, aflibercept, and conbercept has demonstrated promising outcomes in recent years.

Idiopathic choroidal neovascularisation (iCNV) is defined as CNV occurring in patients younger than 50 years without detectable primary ocular or systemic diseases, including PM, angioid streak, trauma, or other inflammatory or hereditary disorders.[10,11] iCNV is a distinct clinical entity that accounts for 17% of cases[12] of CNV in patients less than 50 years old. Treatments including intravitreal and subtenon steroids, transpupillary thermotherapy, surgical removal, and photodynamic therapy with verteporfin[13,14] have varying success in preventing visual loss in patients with iCNV. The visual prognosis and natural progression of iCNV are more favourable than those of CNV in age-related macular degeneration (AMD), and patients suffering from iCNV respond well to anti-VEGF therapy. Anti-VEGF regimens are effective in improving visual acuity, reducing metamorphosis, and reducing central retinal thickness compared to traditional modalities. These anti-VEGF agents have become the first-line treatment for mCNV and iCNV. Conbercept (or KH902, Lumitin; Chengdu Kang Hong Biotech Co, Ltd., Sichuan, People's Republic of China) is an anti-VEGF multitarget drug developed in China for intraocular injection. It can bind to all isoforms of VEGF-A, VEGF-B, and placental growth factors. Conbercept is larger than aflibercept and contains a fourth binding domain of VEGFR-2. It has several advantages, including a lower VEGF dissociation rate, higher binding affinity, lower isoelectric point, and longer clearance time. Since conbercept was approved by the China State Food and Drug Administration (FDA) in 2013 for the treatment of neovascular AMD, diabetic macular oedema, and CNV in pathological myopia, it has become one of the most commonly used anti-VEGF drugs in China.[15–17] Zhang et al.[18] found that conbercept inhibited the VEGF-induced proliferation of human umbilical vein endothelial cells in a dose-dependent manner. Intravitreal injection of high-dose conbercept (300 μg and 500 μg) significantly reduced neovascular leakage, as examined by fluorescence fundus angiography and optical coherence tomography (OCT), and prevented the formation of fibrovascular membranes, as revealed by tissue staining. More importantly, multifocal ERG showed improvement in visual function after the administration of high-dose conbercept. In a cohort study, the same research group demonstrated a significant improvement in the leakage of laser-induced CNV after monkeys in the control group were switched to the conbercept treatment group, suggesting the therapeutic effects of conbercept on pre-existing laser-induced CNV in animals.[19]

As with any general intraocular operation, intravitreal injection of anti-VEGF agents is associated with risks of infection, bleeding, glaucoma, and cataracts.[20] The risk of retinal damage after intravitreal injections is increased in myopic eyes, where degenerative changes at the posterior segment may have already existed.[21] Comprehensive ophthalmic tests should therefore be performed in myopic patients prior to intravitreal injections.

It is now recognised that mCNV can occur at any degree of myopia and in eyes without typical myopic degenerative fundus changes.[22,23] The mechanical theory is based on the assumption that the progressive and excessive elongation of the anteroposterior axis causes mechanical stress on the retina, leading to an imbalance between pro-angiogenic and anti-angiogenic factors, resulting in mCNV.[24] The heredodegenerative theory states that myopic refractive errors are genetically predetermined.[25, 26, 27] In support, studies have shown that single nucleotide polymorphisms in several genes (e.g. pigment epithelium-derived factor) are associated with the development and progression of mCNV.[28 29 30]

This study, we retrospectively reviewed the records of 20 consecutive eyes with mCNV and 18 consecutive eyes with iCNV which were treated with intravitreal conbercept and were followed up for 24 months. All eyes underwent two monthly injections, followed by an additional injection based on monthly visits.

Materials And Methods

This study retrospectively reviewed the charts of patients with CNV between January 2017 and August 2021 at Jinan Central Hospital to determine eligible participants. 20 consecutive subjects with mCNV and 18 with iCNV were included in this retrospective study. The subjects were treated at the retina clinic at Shandong University-affiliated Jinan Central Hospital, a tertiary hospital in Shandong province, China. CNV was diagnosed by clinical examination, OCT, optical coherence tomography angiography (OCTA), and fluorescein angiography and/or indocyanine angiography (ICGA). Exclusion criteria were as follows: patients with AMD, history of ophthalmic operation, history of trauma, patients with previous sub-foveal or juxtafoveal laser treatment, presumed ocular histoplasmosis syndrome, hereditary eye disease, and any other cause of secondary CNV were excluded from the study.

All values are expressed as mean values ± standard deviation. Statistical analyses were performed using SPSS 20.0 (version 20.0; SPSS Inc.). The paired sample t test was used to analyze the post-operative outcome changes compared with baseline values at different time points with a level of $p < 0.05$ being accepted as statistically significant.

Intravitreal Conbercept injection and follow-up

All subjects received intravitreal injection of the anti-VEGF agent conbercept, and the lids and conjunctiva were cleaned with 10% and 5% povidone and iodine, respectively, followed by 1% oxybuprocaine to anaesthetise the conjunctiva. Conbercept (1.0 mg) was injected with a 30 g needle through the pars plana

(4 mm from the limbus) into the vitreous. An eye pad was placed and levofloxacin hydrochloride eye drops were prescribed to be used four times daily for seven days. At each follow-up visit, a thorough ophthalmic assessment was performed, including evaluation of retinal morphology with OCT. If the activity of the lesion could not be determined by clinical evaluation and OCT assessment, fluorescein angiography was performed to document leakage from the ICNV. BCVA, macular appearance, and OCT findings were used to determine whether the patient should have a repeat injection of intravitreal conbercept. A decrease in BCVA, aggravation of metamorphosis, presence of retinal oedema or haemorrhage, increased retinal thickness on OCT, or increased leakage documented on fluorescein angiography prompted additional treatment with conbercept.

Results

All 38 eyes were treated with intravitreal conbercept. The basic information of the two groups was showed in Table 1. Follow-up images were obtained at 1month, 2, 4, 6, 12 and 24months after treatment. The Snellen BCVA was converted to the logarithm of the minimal angle of resolution (logMAR). Most retinal fluid and choroidal neovascularisation within the subretinal space was resolved. Metamorphopsia was reduced. The mean BCVA of group A improved from baseline logMAR 0.31 ± 0.16 to logMAR 0.12 ± 0.03 at the final follow-up(P = 0.000); the mean BCVA of group B improved from baseline at logMAR0.33 ± 0.16 to logMAR0.12 ± 0.03 at the final follow-up(P = 0.000); (Table 2, 3 and Fig. 1).The mean central retinal thickness at the last postoperative visits were reduced from pre-treatment levels of 311.83 ± 30.95μm in group A and 351.17 ± 37.09μm in group B to 229.56 ± 5.75μm and 227.67 ± 4.98μm, respectively (P = 0.000 in group A and P = 0.000 in group B, Table 2, 3 and Fig. 2). The mean CNV area at the last postoperative visits were reduced from pre-treatment levels of 0.83 ± 0.27mm2 in group A and 0.78 ± 0.34mm2 in group B to 0 mm2, respectively (P = 0.000 in group A and P = 0.000 in group B, Table 2, 3 and Fig. 3). Figure 4 presents the CNV changes of a patient with high myopia and choroidal neovascularisation during the follow-up. Figure 5 presents the CNV changes of a patient with iCNV during the follow-up. In our study, the injections were well tolerated by all subjects, with no ocular or systemic complications. The favourable visual and anatomic outcomes achieved lend further confidence in the effectiveness of intravitreal conbercept for the management of myopic CNV and idiopathic CNV.

Table 1
The basic information of the two groups

Indices(Mean ± SD)	Group A (n = 20)	Group B (n = 18)
Age (years)	31.72 ± 4.36	30.22 ± 5.68
SE(D)	-8.12 ± 1.13	-0.91 ± 0.89
Duration of symptoms (months)	0.65 ± 0.37	1.03 ± 0.67
Number of injections	2.22 ± 0.55	2.11 ± 0.47
follow-up duration(months)	24.95 ± 1.03	25.67 ± 1.35
Abbreviations: SD, standard deviation; SE, spherical equivalent		

Table 2
The results of the patients of group A (mCNV) before and after treatment with intravitreal conbercept

Indices (Mean ± SD)	Preoperative	Postoperative					
		1m	2m	4m	6m	12m	24m
BCVA (logMAR)	0.31 ± 0.16	0.15 ± 0.11*	0.13 ± 0.10*	0.11 ± 0.08*	0.11 ± 0.06*	0.13 ± 0.05*	0.12 ± 0.03*
P value	-	0.000	0.000	0.000	0.000	0.000	0.000
CRT(μm)	311.83 ± 30.95	261.50 ± 21.66*	247.06 ± 23.85*	249.78 ± 32.08*	234.83 ± 14.46*	236.28 ± 27.50*	229.56 ± 5.75*
P value	-	0.000	0.000	0.000	0.000	0.000	0.000
CNV area(mm^2)	0.83 ± 0.27	0.22 ± 0.26*	0.06 ± 0.14*	0.02 ± 0.08*	0.01 ± 0.03*	0.03 ± 0.13*	0
P value	-	0.000	0.000	0.000	0.000	0.000	-
BCVA, best-corrected visual acuity; logMAR, logarithm of minimal angle of resolution; CRT, central retinal thickness;CNV, choroidal neovascularization * $p < 0.05$, statistically significant differences compared with preoperation.							

Table 3
The results of the patients of group B (iCNV) before and after treatment with intravitreal conbercept

Indices (Mean ± SD)	Preoperative	Postoperative					
		1m	2m	4m	6m	12m	24m
BCVA (logMAR)	0.33 ± 0.16	0.19 ± 0.11*	0.15 ± 0.08*	0.13 ± 0.06*	0.13 ± 0.04*	0.12 ± 0.03*	0.12 ± 0.03*
P value	-	0.000	0.000	0.000	0.000	0.000	0.000
CRT(μm)	351.17 ± 37.09	289.11 ± 30.05*	256.56 ± 26.16*	234.44 ± 10.42*	239.39 ± 25.61*	232.67 ± 11.99*	227.67 ± 4.98*
P value	-	0.000	0.000	0.000	0.000	0.000	0.000
CNV area(mm^2)	0.78 ± 0.34	0.22 ± 0.21*	0.07 ± 0.13*	0.02 ± 0.05*	0	0	0
P value	-	0.000	0.000	0.000	-	-	-

BCVA, best-corrected visual acuity; logMAR, logarithm of minimal angle of resolution; CRT, central retinal thickness;CNV, choroidal neovascularization. * $p < 0.05$, statistically significant differences compared with preoperation.

Figure 4

Figure 5

Discussion

Intravitreal injection of anti-VEGF agents has become the first-line therapy for mCNV.[9]

The treatment of CNV with anti-VEGF agents promises substantial visual acuity gain and quality of life. In particular, there is now a high level of evidence for the use of conbercept for the treatment of CNV. Intravitreal injection of conbercept for patients with CNV is effective in improving and stabilising vision, and pro re nata(PRN) therapy is effective in controlling disease activity in the long-term. Further research will establish the best management strategy, dosing frequency, and timing of injection and monitoring.

Based on the results of clinical studies and trials, anti-VEGF drugs have demonstrated superior efficacy to traditional modalities, including PDT, LT, and injection of TA, in the treatment of CNV secondary to PM. Therefore, intravitreal injection of anti-VEGF drugs has been proposed as the first-line treatment for CNV secondary to pathological myopia.[9]

Among the anti-VEGF drugs, bevacizumab and ranibizumab exhibit similar efficacy in restoring functional and anatomical parameters. However, ranibizumab is designed and approved specifically for ocular administration and achieves efficacy with a shortened duration and reduced frequency and adverse

effects; hence, it appears to be the first choice for the treatment of myopic CNV when available. Aflibercept and conbercept belong to the new generation of anti-VEGF agents, which are chimeric proteins containing fragments of murine Fab and human Fc, and were originally approved for the treatment of wAMD. Their safety and efficacy in the treatment of myopic CNV need to be confirmed by large-scale rigorous clinical trials.

The standard tests for diagnosing myopic CNV are fundus biomicroscopy, fluorescein angiography (FA) and OCT. FA and OCT are generally recommended baseline diagnostic tests for myopic CNV in conjunction with colour photos and clinical examination. OCT is a non-invasive, interferometric imaging modality that enables in vivo imaging of the retina in cross-section. OCT has radically changed the diagnostic approach for macular diseases by offering a non-invasive imaging method that is highly sensitive in identifying retinal and subretinal abnormalities associated with both CNV and subretinal fluid.[31,32] OCTA is a new imaging technique based on OCT which allows for the visualisation of functional blood vessels in the eye. The principle of OCTA is to use the variation in the OCT signal caused by moving particles, such as red blood cells, as the contrast mechanism for imaging blood flow.

In a non-invasive manner, OCTA allows visualisation of the retinal and choroidal vasculature in three dimensions without any dye injection[33–39].OCTA are derived from repeated structural B-scans; therefore, they are perfectly co-registered with morphological data. OCTA enables a simultaneous assessment of structural and functional retinal or choroidal features. OCTA identifies features of mCNV secondary to pathological myopia and has demonstrated its high sensitivity and specificity for neovascular detection. OCTA could be a useful alternative tool that clinicians could use to evaluate patients with high myopia, especially those patients with a history of allergic reaction. In our study, all the patients accepted OCTA follow-up without ICGA or FFA; it is a totally non-invasive, efficient, and effective follow-up method, and the systemic side effects of indocyanine green fluorescein sodium use are avoided. OCTA clearly showed the changes of neovascularisation and guided the treatment.

The results of other successful trials,[40–44] showed that the dosing regimen of choice for intravitreal ranibizumab 0.5 mg for mCNV has been established as a single injection followed by PRN (1 + PRN). Treatment benefit in mCNV, followed for 12 months, has been documented with a single injection.[45]

Studies that used an alternative loading-dose protocol of 3 initial monthly ranibizumab 0.5mg injections (3 + PRN) found outcomes comparable to those of the 1 + PRN regimen.Although patients following a 3 + PRN regimen received a higher number of total injections over the treatment period (over 12 months), the re-treatment rate in the PRN phase was lower compared with patients following a 1 + PRN regimen.[46–48]

In this study, we used the conbercept 0.5mg2 + PRN scheme to observe the regression of neovascularization. The patients who used the 2 + PRN scheme were followed up for 24 months. Results show that conbercept has a significant effect in the treatment of mCNV and iCNV. The neovascularization subsides and the central retinal thickness is significantly reduced. Two injections + PRN regimen can be

used to treat mCNV and iCNV.The application of noninvasive OCTA can well follow up the regression of neovascularization.

The results showed that the regression of neovascularization was ideal, the visual acuity was improved and stable, and the retinal edema was well subsided. The advantages of our study include: the follow-up time is relatively long compared with other studies and the condition is stable after 2 + PRN scheme.

Our study has several limitations. First, its retrospective nature makes the standardisation of patient treatments and follow-up difficult. Variability in the number of injections is largely dependent on the primary physician, and the initial visual acuity(VA) plays a significant role.

Abbreviations

OCTA: Optical coherence tomography angiography; mCNV:myopic choroidal neovascularisation ; iCNV: idiopathic choroidal neovascularisation; BCVA:best-corrected visual acuity ; PM :pathologic myopia; anti-VEGF:anti-vascular endothelial growth factor; AMD:age-related macular degeneration; OCT: optical coherence tomography ; ICGA:indocyanine angiography; CRT:central retinal thickness. PRN: pro re nata

Declarations

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None

Authors' contributions

Yanlei Hao and Wei Zhu are co-first authors who contributed equally to this work. Design of the work(H.C.M.); Drafting the work and substantively revision(H.Y.L. and Z.W.) acquisition, analysis(Y.Z.F. and L.J.H.), interpretation of data(M.Y.).

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Availability of data and materials

All the data of this study are included within the article and are available from the corresponding author upon reasonable request.

Declarations 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. Written Informed Consent was

obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no confict of interest.

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Figures

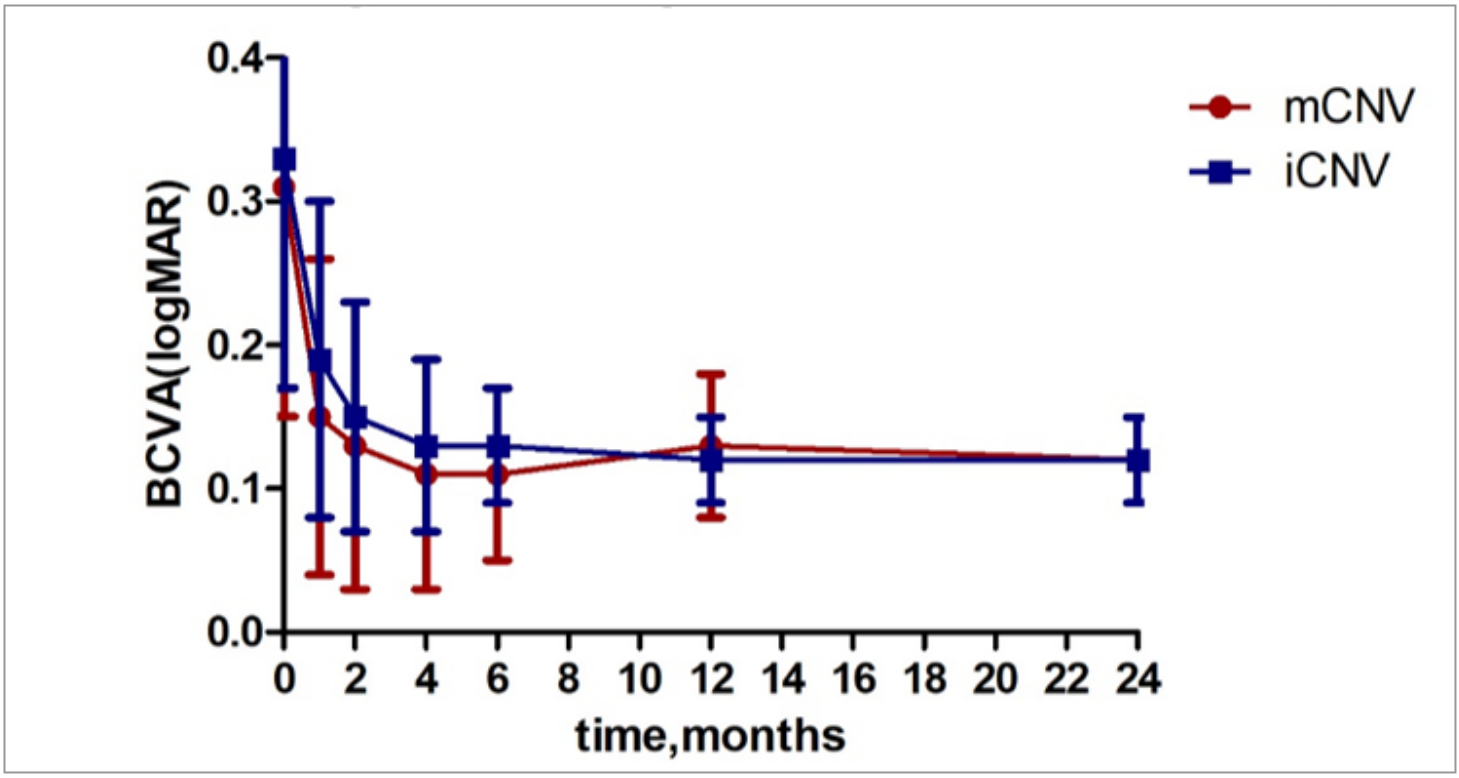

Figure 1

BCVA changes following treatment with conbercept

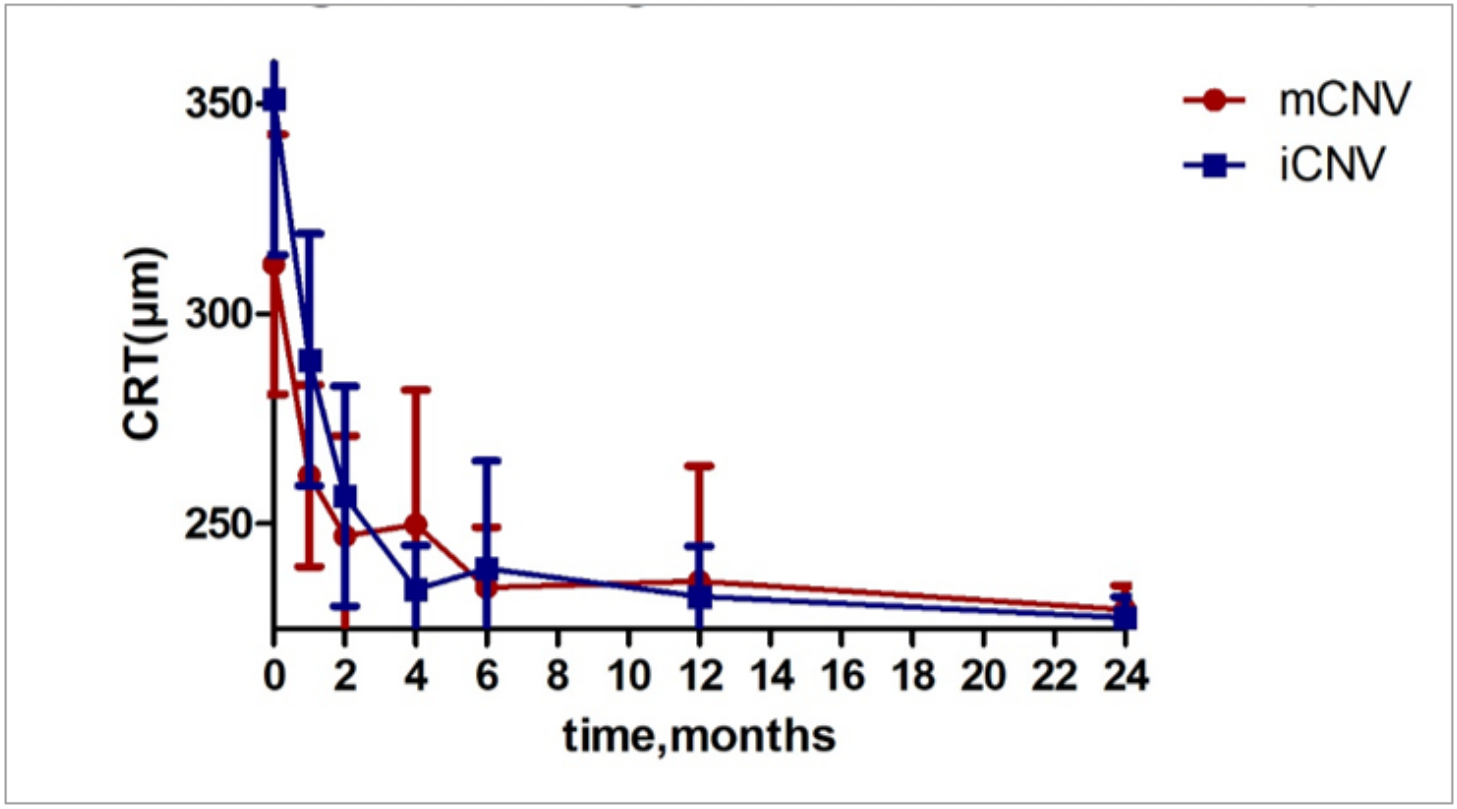

Figure 2

CRT changes following treatment with conbercept

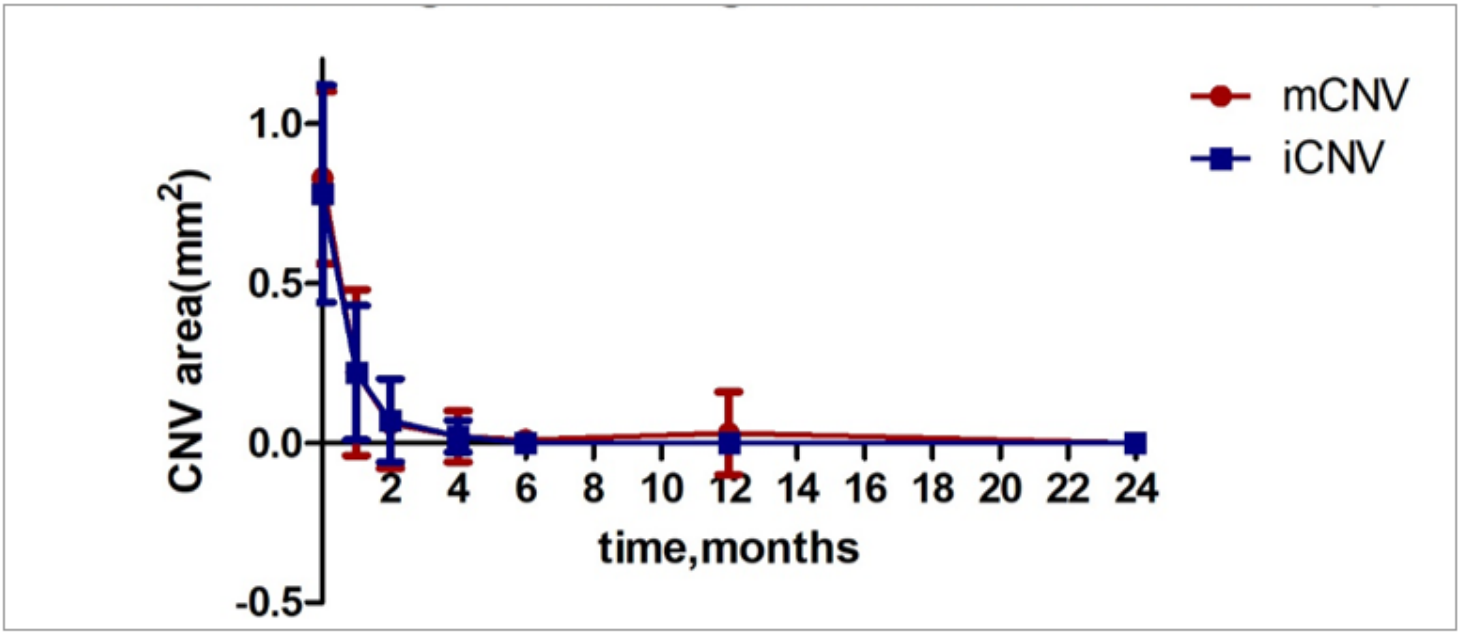

Figure 3

CNV area changes following treatment with conbercept

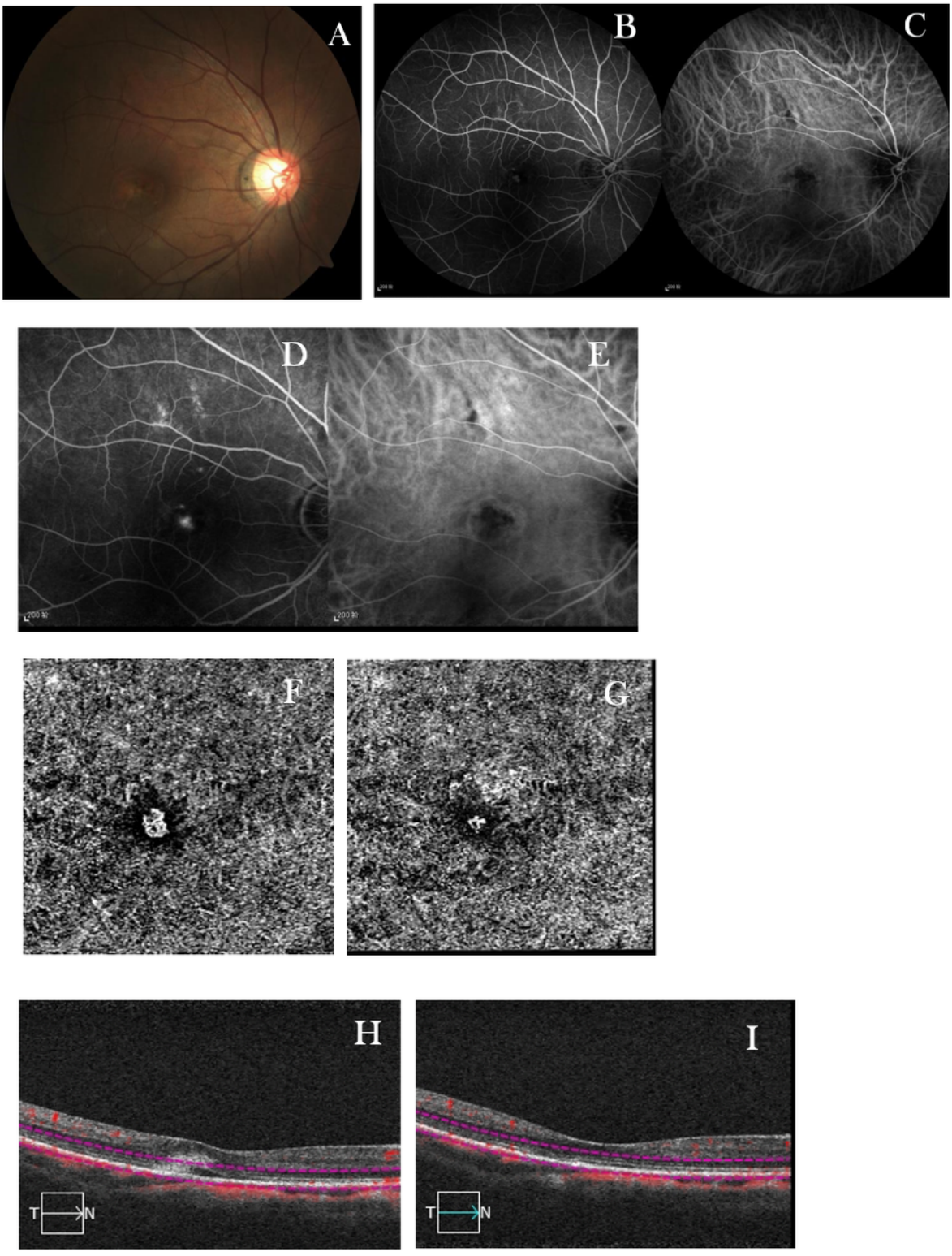

Figure 4

Case of a 34-year-old male patient presenting with high myopia and choroidal neovascularisation. (A)Fundus photo of the right eye with mCNV showing presence of a subretinal greyish exudation. (B,C) Early fluorescein angiography and indocyanine green angiography (ICGA). (D,E) Late fluorescein angiography and indocyanine green angiography (ICGA), late phase fluorescein angiography (FFA) showing leakage due to mCNV. (F) OCTA at diagnosis. (G) OCTA at first conbercept injection 35 days later, CNV regressive. (H) B-scan at diagnosis. (I) B-scan at first conbercept injection 35 days later, CNV regressive, retinal thickness decreased.

Figure 5

Case of a 29-year-old female patient presenting with choroidal neovascularisation, diagnosed with iCNV. (A) OCTA shows CNV at diagnosis. (B)OCTA showed CNV regressive after the first conbercept injection. (C)OCTA showed CNV regressive after the second conbercept injection. (D) En-Face at diagnosis. (E) En-Face after the first conbercept injection. (F) En-Face after the second conbercept injection. (G) B-scan at diagnosis. (H) B-scan after the first conbercept injection, CNV regressive and retinal thickness decreased. (I) B-scan after the second conbercept injection showed that CNV disappeared and retinal thickness returned to normal nearly. Ellipsoid zone with discontinuity