·Clinical Research·

Optical coherence tomography characteristics of responses to intravitreal bevacizumab in idiopathic choroidal neovascularization

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Abstract

• AIM: To investigate factors associated with responses to intravitreal bevacizumab (IVB) in naive idiopathic choroidal neovascularization (iCNV) by high domain optical coherence tomography (OCT).

• METHODS: We retrospectively reviewed clinical data of 40 eyes of iCNV patients who received a single or multiple IVB on an as-needed basis (1.25 mg/0.05 mL). One month after the first injection, subretinal fluid (SRF) volume was evaluated and the eyes were divided into 3 groups based on responses to IVB. Good, moderate, and poor responses were defined as 61%-99%, 30%-60%, and <30% resolution of SRF on OCT after IVB in iCNV, respectively. OCT findings were analyzed to find factors associated with difference in response levels. Comparisons were made using Wilcoxon´s matched-pairs signed-rank test, the Mann-Whitney *U* test for means with continuous data and Fisher´s exact test for categorical data.

• RESULTS: The mean number of IVB was 1.28±1.50 and mean follow up time was 3.60±1.20mo. At postoperative 1mo, there were 8 (20%) eyes in good response, 20 (50%) in moderate response and 12 (30%) eyes in poor response group and at last visit there were 28 good responders (70%), 8 (20%) moderate responders and 4 (10%) poor responders. Statistically significant difference was detected between good responders and non good responders in choroidal neovessels thickness (*P*=0.029), SRF height (*P*=0.049) and SRF volume (*P*=0.031) at post treatment 1mo.

• CONCLUSION: OCT is a valuable diagnostic tool. Decrease in choroidal neovessels thickness, SRF height and volume predicts favorable response of iCNV to IVB therapy.

• **KEYWORDS:** bevacizumab; idiopathic choroidal neovascularisation; optical coherence tomography; subretinal fluid

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INTRODUCTION

Idiopathic choroidal neovascularization (iCNV), a unilateral ocular disease which occurs in patients younger than 50y and diagnosed when the cause of choroidal neovascularization (CNV) is undetermined and accounts for approximately 17% of patients with CNV [1-3]. These neo-vessels are derived from the choroidal vasculature and penetrate through Bruch's membrane into the subretinal space which is a typical presentation of type 2 CNV[4]. Leaky nature of these vessels in macular region leads to disturbance in the fluid outflow between the sensory retina and Bruch's membrane which result in separation of basement membrane and inner collagenous layer, referred as retinal pigment epithelial detachment and varying degree of retinal pigment epithelial changes[5].

Various treatments, including photodynamic therapy (PDT), anti-vascular endothelial growth factor (anti-VEGF) have been used to promote the remission of subretinal fluid (SRF) in iCNV [6-8]. Intravitreal bevacizumab (IVB), a recombinant humanized monoclonal anti-VEGF antibody, has been reported to be effective in iCNV patients. Recently several studies have clarify retinal microstructural changes, choroidal thickness and visual acuity improvement in iCNV eyes after application of anti-VEGF as treatment therapy [6]. Various reports have shown that bevacizumab (Avastin; Genetech, Inc.), achieved significant visual effects in treating iCNV[7]. However, there appears to be variation in treatment responses to IVB and unknown factors that could predict variable response to this treatment[8-13].

We achieved variable response in our iCNV patients after IVB therapy. Therefore, we investigate clinical outcomes of a single or multiple successive IVBs for treatment-naive iCNV

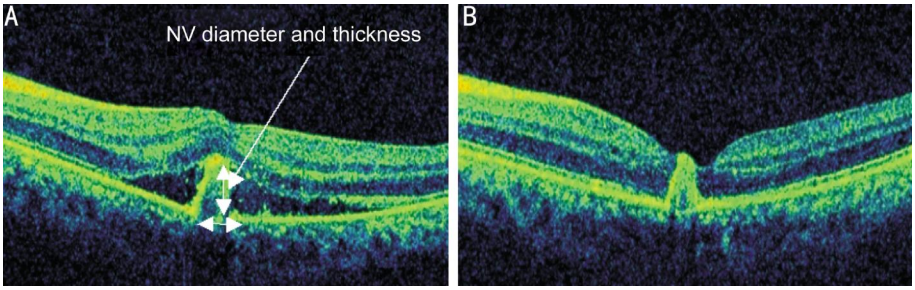

Figure 1 Parameter measurement on OCT in iCNV patients SRF dissolved after application of IVB, leading to intact retinal layers architecture. NV: Neovascularization.

patients, focusing on optical coherence tomography (OCT) prognostic factors associated with resolution of SRF.

SUBJECTS AND METHODS

This retrospective observational study was approved by the Institutional Review Board of Xi'an Jiaotong Medical University. We reviewed charts of forty patients who received IVB (1.25 mg/0.05 mL Avastin; Genentech, Inc, San Francisco, CA, USA) for iCNV between September 2013 and September 2014 and were followed up for more than 6mo in the Department of Ophthalmology. The study was conducted according to the Declaration of Helsinki.

Patients were younger than 50y and showed active CNV by ophthalmoscopy, slit-lamp biomicroscopy, fluorescein/indocyanine angiography and OCT. Active stage of iCNV was defined as leakage within the macular lesion by fluorescein/indocyanine angiography and associated with SRF, and retinal pigment epithelial detachment based on Cirrus high domain-optical coherence tomography (HD-OCT). We excluded patients with CNV because of pathological myopia (refractive error ≥-6 D or axial length ≥26 mm), clinical signs of macular degeneration, angioid streaks, presumed ocular histoplasmosis syndrome (POHS), uveitis, traumatic choroidal rupture, hereditary and macular diseases and undergone previous treatment of intravitreal anti-VEGF injection, surgery, laser photocoagulation or photodynamic therapy. Best-corrected visual acuity (BCVA), slit-lamp biomicroscopy and OCT were obtained at every single visit in all patients. The BCVA was recorded using the decimal chart and was converted to the logarithm of the minimum angle of resolution (logMAR) equivalents.

Optical Coherence Tomography In this study we have used Cirrus HD-OCT with data acquisition rates of up to 27 000 axial scans/s, and macular cube (512A-scans×128B-scans over a 6×6-mm^2 area centered on the fovea) volume. We applied OCT calipers manually to calculate volume of SRF by using Heussen *et al* [14] method to the HD-OCT acquired images. B-scan (vertical) counts and A-scan (horizontal) counts were determined by identifying the first and last scans containing SRF. The difference between the numbers of the first and last scans constituted the number of scans involved in the measurement. Thus, difference in A-scan line equals the change in horizontal dimension of lesion and difference in B-scan line equals the change in vertical dimension of lesion [14] (SRF volume=difference in A-scan line×difference in B-scan line×maximum SRF height).

For the purpose of this study, SRF on OCT was defined as homogeneous hyporeflective space between neurosensory retina and RPE [15]. We defined resolution of retinal fluids as absence of SRF evaluated on OCT scans. The diameter of CNV was defined as the maximum horizontal margin that could be distinguished by OCT [15]. Thickness of CNV was defined as the maximum CNV thickness above the retinal pigment epithelial level that could be determined by hyper-reflectivity [15]. The above defined parameters were measured manually with the caliper function included in the OCT software (Figure 1). Central subfield thickness (CSFT) was measured by the automatic algorithms defined as mean retinal thickness of 1-mm center as described in the Early Treatment Diabetic Retinopathy Study and measured by the automatic algorithms.

Outcome Variables Effects of IVB were evaluated by primary outcome variables including BCVA (logMAR), SRF volume, CSFT, and secondary outcome variables including choroidal neovessels thickness and diameter. Good responders were defined as 61%-99% resolution of SRF on spectral domain OCT. Moderate responders were defined as SRF resolution of 30%-60% of baseline volume and poor responders as SRF resolution <30%.

Statistical Analysis Statistical analyses were performed using SPSS for Windows (version 20.0; SPSS, Inc., Chicago, IL, USA). logMAR was calculated from decimal visual acuity for statistical analysis. Data were expressed as mean ±SD. Descriptive statistics for all demographic and clinical variables were calculated, and comparisons were made using Wilcoxon's matched-pairs signed-rank test, the Mann-Whitney *U* test for means with continuous data and Fisher's exact test for categorical data. *P* values less than 0.05 were considered significant.

RESULTS

Forty eyes of 40 subjects were included. The mean age was 30.1±7.8y. Twenty-eight patients were female. During the mean follow-up of 3.60±1.20mo, the mean number of IVB

Table 1 Effects of IVB on outcome variables from baseline to last visit in iCNV patients *n*=40

Variables	Baseline	One month after 1st IVB	*P*	Last visit	*P*
BCVA (logMAR)	0.65±0.17	0.52±0.16	0.064	0.15±0.88	<0.001
SRF height (μm)	148.20±59.0	99.20±47.50	<0.001	56±19.31	<0.001
SRF volume (μm^3)	3.20±1.3	1.10±6.1	<0.001	0.64±4.6	0.002
CSFT (μm)	364.75±125.80	338.70±40.0	0.835	256.03±27.80	<0.001
CNV thickness (μm)	348.75±137.20	180.45±52.00	<0.001	83.20±28.10	<0.001
CNV diameter (μm)	460.50±136.0	196.10±109.22	<0.001	209.73±106.30	<0.001

BCVA: Best-corrected visual acuity; IVB: Intravitreal bevacizumab; SRF: Subretinal fluid; logMAR: Logarithm of minimal angle of resolution; CSFT: Central subfield thickness; CNV: Choroidal neovascularization.

Table 2 Clinical features associated with response to IVB at postoperative 1mo and last visit

Parameters	Overall	One month after first IVB			Last visit		
		GR (*n*=8)	NGR (*n*=32)	*P*	GR (*n*=27)	NGR (*n*=13)	*P*
Age (a)	30.1±7.8	28.3±5.32	33.9±10.7	0.033	31.80±9.56	28.40±5.24	0.171
M/F	12/28	1/7	11/21	0.323	9/18	3/10	0.057
Refractive error	-2.50±2.24	-1.75±1.25	-1.50±1.30	0.723	-1.25±0.75	-1.50±1.11	0.674
BCVA (logMAR)	0.65±0.17	0.40±0.14	0.50±0.20	0.574	0.16±1.06	0.20±0.23	0.433
SRF height (μm)	148.17±59.04	82.00±49.20	104.80±45.50	0.049	29.51±14.58	49.23±10.72	<0.001
SRF volume (μm^3)	3.2±1.3	0.83±0.51	1.16±0.48	0.031	0.367±0.26	0.480±0.21	0.051
CSFT (μm)	364.75±125.8	329.60±40.22	347.75±38.62	0.154	256.40±26.2	255.3±32.21	0.965
CNV thickness (μm)	348.75±137.2	138.30±57.4	182.60 ±52.0	0.029	42.40±27.10	44.86±28.63	0.751
CNV diameter (μm)	460.50±136.0	189.90±101.5	202.95±90.20	0.597	210.40±132.6	207.12±89.9	0.459

BCVA: Best-corrected visual acuity; logMAR: Logarithm of minimal angle of resolution; SRF: Subretinal fluid; CSFT: Central subfield thickness; CNV: Choroidal neovascularization; GR: Good responsers; HGR: Non-good responsers.

was 1.28±1.50. None of the eyes developed serious injection-related complications such as endophthalmitis and systemic complications. At last visit after first IVB, there were 28 good responders (GRs) (70%), 8 (20%) moderate responders (MRs) and 4 (10%) poor responders (PRs) patients. The mean baseline BCVA (logMAR) was 0.65 ±0.17 which showed significant improvement BCVA (logMAR) 0.15±0.88; P< 0.001. Beside significant visual improvement, SRF height decreased by 62.1% (P <0.001), SRF volume by 80.0% (P=0.002), CSFT by 29.8% (P<0.001), choroidal neovessels thickness by 76.1% (P <0.001) and 54.5% (P <0.001) diameter (Table 1).

Subgroup analysis showed that visual improvement did not show any statistical significance between the good responders and non good responders (moderate and poor). We further evaluate the clinical outcome at 1mo after the first IVB to better understand the short-term effect of bevacizumab on iCNV patients. After a single session of IVB, 8 (20%) patients achieved good responses, whereas 20 (50%) patients showed moderate responses, and 12 (30%) patients showed poor responses. Overall, there was no visual improvement BCVA (logMAR) of 0.65 ±0.17 to 0.52 ±0.16; P =0.064. However, SRF height significantly decreased by 33.0%(P< 0.001), SRF volume by 65.6% (P<0.001), choroidal neovessels thickness by 48.3% (P <0.001) and choroidal neovessels diameter by 57.4% (P <0.001). CSFT did not show any significant change (Table 1). Analysis of OCT features were conducted between GR and MR/PR patients (Table 2). Statistically significant difference was detected between GRs and non-good responders in choroidal neovessels thickness (P=0.029), SRF height (P = 0.049) and SRF volume (P = 0.031) at post treatment 1mo.

DISCUSSION

The pathological basis of iCNV and age-related macular degeneration (AMD) are similar; both present as CNV in the macular region and cause bleeding, oozing, and fibrous scarring [16]. These pathological changes are closely related to VEGF expression. IVB can be an attractive treatment option of iCNV. Several studies have evaluated the efficacy of IVB for iCNV, showing beneficial visual outcome and high safety profile [6-10]. Some patients responded well to this drug while others responded poorly[17-19].

In the present study, 20% of iCNV patients with SRF showed good absorption within 1mo after a single session of IVB. At last follow up, 70% of patients achieved good resolution, with mean follow up of 3.6mo and mean number of 1.28±1.50 IVBs. Zhang *et al* [10] have followed a cohort of 40 patients for 12mo and the mean number of IVB treatments were 2 injections per eye during 12mo follow-up, resulting in all lesions converting to the cicatricial stage; In their study, after single IVB 40% of patients have complete resolution of subretinal fluid and 70% had complete resolution of subretinal fluid after additional injection. The reason for this difference is not clear, but in our study we have included patients with the baseline BCVA (logMAR 0.65 *vs* 0.53) and hence we have lower percentage (20% *vs* 40%) resolution after single IVB.

Decrease in choroidal neovessels thickness finding is in agreement with Shin *et al* [15] and Framme *et al* [20] in exudative age related macular degeneration patients that reported significant decrease in choroidal neovessels thickness after application of anti-VEGF. Considering short half-life of bevacizumab that remains in the eye for 4-6wk, we analyze clinical results at 1mo after single IVB treatment[21]. Decrease in choroidal neovessels thickness, SRF height and SRF volume was an interesting finding and, to the best of knowledge, has not been reported in iCNV studies.

Treatment scheme for iCNV has yet not been established. iCNV have good prognosis naturally, as indicated by Ho *et al* [4]. In their study, 95% of the patients have same or better visual acuity as compared to initial vision. Similar reports exist regarding the prognosis of iCNV in young patients. There is no controlled trial about this subject and most researches included only one injection [8,10]. A benefit from the treatment hasn't been shown in whether controlled or uncontrolled trials. As stated in 1995, it appears that iCNVs are mostly benign and the follow up is as effective as therapy. Our study showed that therapy doesn't benefit and poor responders showed better visual acuity. So treatment is not mandatory in all cases and pros and cons should be considered when the decision to treatment is to be made, because treatment is not far from the complications, some of which are serious.

Shortcomings of this study need to be highlighted including its retrospective nature, absence of control group and relatively small number of patients. Several study parameters, including size of choroidal neovessels thickness and diameter, SRF height, change in B-scan and A-scan were measured manually due to absence of automated software. However, we noted a clear trend toward short-term favorable response to IVB in iCNV could be predicted in eyes with less choroidal neovessels thickness and SRF height. This finding and our clinical results may aid clinicians to better select and schedule treatment plans in managing iCNV patients.

We concluded that IVB injection improve visual acuity and well tolerated in iCNV patients. Decrease in choroidal neovessels thickness, SRF height and volume predicts favorable response of iCNV to IVB therapy.

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