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Original Article

Association between subfoveal choroidal thickness and prognoses after anti-vascular endothelial growth factor therapy in myopic choroidal neovascularization

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Abstract: *Purpose:* The aim of this study was to investigate subfoveal choroidal thickness (SFCT) changes following intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy and to identify SFCT and clinical parameters associated with functional anatomical prognoses in eyes with myopic choroidal neovascularization (mCNV). *Methods:* Forty-five pathologic myopia patients with unilateral mCNV (45 eyes) were enrolled in the study. All patients were treated with a single intravitreal injection of bevacizumab or ranibizumab by Pro Re Nata regimen. All subjects were evaluated by Spectral domain optical coherence tomography (SD-OCT) at baseline, one month, three months, and final visit after treatment. *Results:* Anti-VEGF therapeutics revealed significantly improved best-corrected visual acuity (BCVA), significantly decreased central foveal thickness (CFT), and greatest linear dimension (GLD) (all $P < 0.05$). SFCT revealed a significant decrease ($P < 0.05$) after anti-VEGF treatment. In multivariate regression analysis, baseline BCVA and recurrence associated significantly with final BCVA ($P < 0.001$ and $P = 0.002$, respectively). Baseline GLD and recurrence were associated significantly with final GLD ($P = 0.001$, respectively). In generalized linear model (GLM) analyses, number of injections was associated with recurrence ($P = 0.001$). However, SFCT was not associated with final BCVA, GLD, and number of injections. *Conclusion:* Anti-VEGF regimen was proven to be effective on mCNV, probably arousing significant changes in choroidal thickness. However, SFCT was not associated with functional and anatomical prognoses.

Keywords: Myopic choroidal neovascularization, subfoveal choroidal thickness, spectral-domain optical coherence tomography, anti-vascular endothelial growth factor

Introduction

Myopic choroidal neovascularization (mCNV) is a major sight-threatening complication of pathologic myopia. It has a poor prognosis without treatment [1-4]. It has been estimated that 5%-11% of patients with pathologic myopia (PM) develop choroidal neovascularization (CNV) [4, 5]. Myopic CNV often affects adults of working age [1], accounting for 62% of CNV cases in patients younger than 50 years of age, having a significant impact on patient quality of life [6]. Risk factors and the pathogenesis of mCNV are not well understood [7]. Recently, studies have presented evidence of a pathogenic association between choroidal thickness (CT) and mCNV. The findings of Ikuno and Maruko's studies suggest that pronounced mechanical stretching and associated choroidal thinning play a role in the development of mCNV [7, 8]. As anti-vascular endothelial growth factor (anti-VEGF) treatment has replaced photodynamic therapy (PDT) as a first-line therapy for mCNV, concerns have been raised regarding whether progressive thinning of choroid may develop after anti-VEGF therapy, leading to visual impairment [9].

Vascular endothelial growth factor (VEGF) is a cytokine that physiologically and pathologically occurs in the retina as well as many other tissues and organs throughout the body. VEGF induces vessel dilation and increases ocular blood flow through a mechanism involving increased nitric oxide (NO) production by its vasodilatory effects [10, 11]. One possible ocular adverse effect of anti-VEGF agents may, therefore, carry the risk of induced ischemia,

through blockage of the action of VEGF on ocular vessels and blood flow through its vasodilatory effects [12, 13]. Recent reports have shown that both bevacizumab and ranibizumab are associated with ischaemic retinal and choriocapillaris changes and reduce retrobulbar blood flow and arteriolar vasoconstriction following its intraocular administration in neovascular age-related macular degeneration (AMD) and branch retinal vein occlusion, suggesting circulatory disturbances as a consequence of treatment [14-16].

Apart from the benefits of anti-VEGF agents regarding mCNV, it remains unknown whether it is associated with ischemia of choroidal capillaries and affect choroidal thickness. However, changes of CT after anti-VEGF therapy and the relationship of CT with visual outcomes after anti-VEGF therapy have not been well documented in patients with mCNV [9, 17-19]. Visual outcome is the most important functional prognoses in treatment of mCNV. To the best of our knowledge, there are no reports concerning the relationship of CT with anatomical outcomes after anti-VEGF therapy. Thus, a consecutive series of patients with mCNV were studied to evaluate SFCT changes after anti-VEGF treatment and its relation to final BCVA, greatest linear dimension (GLD) of CNV, and number of injections.

Subjects and methods

Subjects

This retrospective study included 45 eyes from 45 consecutive pathologic myopia patients with unilateral mCNV, visiting Jinan Mingshui Eye Hospital between August 2013 and September 2016. All patients were treated with intravitreal injections of an anti-VEGF agent, either bevacizumab (Avastin; Roche; 1.25 mg) or ranibizumab (Lucentis; Novartis; 0.5 mg) on the first visit, followed by Pro Re Nata (1+PRN) injections. They were followed up for at least 3 months. This study was performed in accordance with tenets of the Declaration of Helsinki and was approved by the local institutional Ethnics Committee of Jinan Mingshui Eye Hospital.

Inclusion criteria were (1) Bilateral pathological myopia, defined as spherical equivalent of less than -6 diopters (D) or axial length more than 26 mm, with typical degenerative changes of pathological myopia; and (2) Active subfoveal or juxtafoveal CNV confirmed with fundus fluorescein angiography (FFA). Patients were excluded from this study if they had any of the following: (1) History of intraocular injections, or PDT; (2) Presence of other macular diseases, such as vitreomacular traction, foveoschisis, macular hole, epiretinal membrane, or AMD; (3) Severe cataracts that could affect visual acuity or image quality; and (4) History of severe systemic problems. Eyes with mCNV served as the study group and fellow uninvolved eyes were grouped under the control group.

Examinations

At baseline, all participants received comprehensive ophthalmologic examinations, including reviews of their medical and clinical histories. Best-corrected visual acuity (BCVA) was measured using a standard decimal visual acuity chart. Patients also received slit-lamp biomicroscopy examinations, refractive error, measurements of axial length, color fundus photography, FFA and indocyanine green angiography (ICGA, HRA-2, Heidelberg Engineering, Heidelberg, German), and spectral domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany). BCVA were converted to a logarithm of minimal angle resolution (logMAR) equivalent for statistical analysis. GLD of CNV was measured on OCT images with internal caliper software. Classification of myopic maculopathy in the color fundus photographs was made by 2 investigators, independently, in accordance with progression patterns proposed by Hayashi et al. [5]: tessellated fundus, diffuse chorioretinal atrophy, patchy chorioretinal atrophy, presence of lacquer cracks, and macular atrophy.

Treatment

All patients were treated with a single intravitreal injection of 1.25 mg bevacizumab (Avastin; Roche) or 0.5 mg ranibizumab (Lucentis; Novartis) at baseline. Treatment was not altered by entrance into the study. Additional injections were subsequently administered on a monthly basis (pro-re-nata regimen) until mCNV was inactive. Retreatment was administered for recurrent or aggravated intra/subretinal fluid on OCT. All patients underwent follow up examinations for at least 3 months and were reviewed

Table 1. Clinical Characteristics of affected eyes (study group) and fellow unaffected eyes (control group)

Characteristic	mCNV eyes	Fellow eyes	t	*P* value
Number of eyes	45	45	-	NA
Age (year)	48.71 ± 8.89	48.71 ± 8.89	-	NA
Sex (men/women)	13/32	13/32		NA
Follow-up duration (month)	10.02 ± 1.05	-	-	NA
Number of injection	2.56 ± 1.63	-	-	NA
Location of CNV, subfoveal: juxtafoveal	43/2	-	-	NA
Drugs used for injection, Bevacizumab: ranibizumab	20/25	-	-	NA
Time to recurrence (month)	12.56 ± 6.39	-	-	NA
Axial length (mm)	27.98 ± 1.73	27.87 ± 1.80	0.300	0.764
Refractive error (D)	13.62 ± 5.55	13.39 ± 5.51	0.190	0.848
CFT (μm)	366.49 ± 167.66	207.62 ± 55.54	6.030	< 0.001
SFCT (μm)	65.27 ± 45.81	66.80 ± 30.75	0.190	0.853

NA, not applicable; mCNV, myopic choroidal neovascularization; CNV, choroidal neovascularization; CFT, central foveal thickness; SFCT, subfoveal choroidal thickness.

at 1 month, 3 months, and final visit during which BCVA and SD-OCT were repeated. For patients with symptoms or signs of CNV aggravation, FFA was also performed. Additional visits were on an as-needed basis.

Measurement of SFCT and CFT

Full-thickness choroidal images were obtained using SD-OCT with eye-tracking and image-averaging systems. Horizontal sections passing through the foveal center were used for measurements of SFCT. Choroidal thickness was measured manually with calipers as the distance from the outer border of the retinal pigment epithelium (RPE) to the inner surface of the sclera. All measurements were performed by two independent and experienced investigators masked to patient information. An average of the two measurements was recorded for analysis. Central foveal thickness (CFT) was manually calculated at the fovea by horizontal scan, measuring the distance between Bruch membrane and the internal limiting membrane. If measurements differed by greater than 15%, a final measurement was agreed after open arbitration by a third senior examiner. Enhanced-depth imaging (EDI) was not used but all eyes still showed clear interface because of choroidal thinning.

Statistical analyses

Statistical analyses were performed using SPSS version 21.0 (SPSS for windows, SPSS Inc., Chicago, IL). Distribution of normality was assessed using Shapiro-Wilk test. Independent t-test was performed comparing continuous variables between independent groups. Repeated measure was used for comparisons between baseline, one month, three months, and final visit for continuous variables. Univariate and multivariate regression analyses were performed to identify factors associated with final BCVA, GLD, number of injections. *P* values less than 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

This study included 45 patients of bilateral pathological myopia with unilateral mCNV, comparing mCNV eyes (study group) with fellow eyes (control group). Baseline clinical data of all eyes are presented in **Table 1**. The majority of the patients were women (n = 32) and the mean age was 55.31 ± 12.65 years. Subfoveal and juxtafoveal CNV were present in 43 (95.56%) and 2 (4.44%) eyes, respectively. Mean follow up period was 10.02 ± 1.05 months. Mean number of injections during the follow up period was 2.56 ± 1.63 (range, 1-10). Time to recurrence ranged from 3 to 24 months with a mean of 12.56 ± 6.39 months. CFT was thicker in the study group. This was statistically significant when compared with the control group. There were no significant differences in SFCT between the two groups.

Table 2. Changes in mean BCVA, CFT, GLD, and SFCT of the study group during the follow up period (n = 45)

Parameter	Baseline	1 month	3-month	Final visit	F	*P* Value
LogMAR	1.32 ± 0.38	1.08 ± 0.33(a)	1.02 ± 0.32(a,b)	1.12 ± 0.38(a,c)	0.641	< 0.0001
CFT	366.49 ± 167.66	276.13 ± 122.41(a)	256.31 ± 110.89(a,b)	269.71 ± 147.98(a)	0.809	< 0.0001
GLD	1928.60 ± 995.16	1372.47 ± 795.93(a)	1170.49 ± 734.69(a,b)	1360.53 ± 830.19(a)	19.598	< 0.0001
SFCT	65.27 ± 45.81	56.91 ± 39.76(a)	53.13 ± 38.27(a,b)	51.69 ± 37.97(a,b)	21.567	< 0.0001

a: P < 0.05 comparing with baseline; b: P < 0.05 comparing with 1 month; c: P < 0.05 comparing with 3-month; BCVA, best-corrected visual acuity; CFT, central foveal thickness; GLD, greatest linear dimension; SFCT, subfoveal choroidal thickness; LogMAR, logarithm of minimal angle resolution.

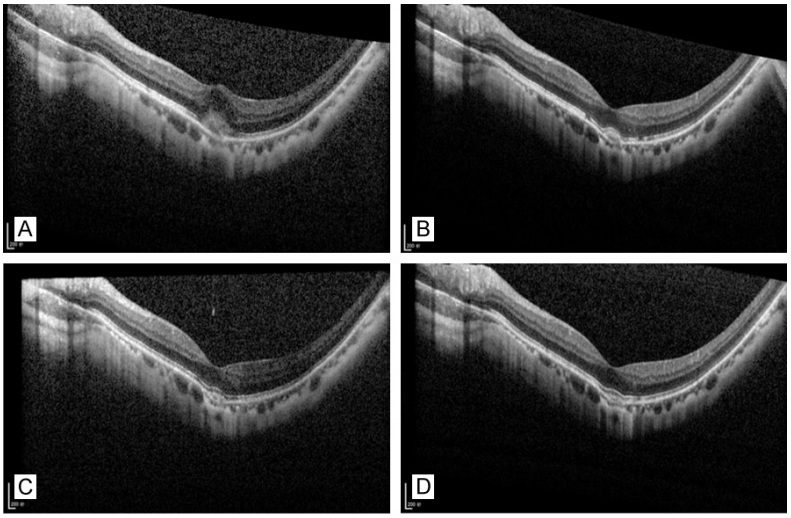

Figure 1. Long-term course of choroidal thickness changes on spectral domain optical coherence tomography (SD-OCT) after intravitreal ranibizumab injection (IVR) in the left eye of a 57-year old woman with myopic choroidal neovascularization (mCNV). Subfoveal choroidal thickness (SFCT) decreased from 74 mm at baseline (A) to 64 mm at 1 month (B), 58 mm at three months (C), and 41 mm at six months (D) after IVR.

Changes of BCVA, CFT, GLD, and SFCT on SD-OCT

Mean BCVA improved significantly at 1 month, 3-months, and final visits compared with baseline, from 1.32 ± 0.38 logMAR at baseline, to 1.08 ± 0.33 logMAR at 1 month (*P* = 0.059), 1.02 ± 0.32 logMAR at 3-months (*P* = 0.002), and 1.12 ± 0.38 logMAR at final visit (*P* = 0.003, **Table 2**). BCVA also improved from 1 month to 3-months (P < 0.0001) but not thereafter (P = 0.277). Patients had worse BCVA at final visit compared with 3-months (P < 0.05, **Table 2**).

Mean CFT was significantly reduced at 1 month, 3-months, and final visits compared with baseline, from 366.49 ± 167.66 μm at baseline, to 276.13 ± 122.41 μm at 1 month (P = 0.059), 256.31 ± 110.89 μm at 3-months (P = 0.002), and 269.71 ± 147.98 μm at final visit (*P* = 0.003, **Table 2**). CFT was also significantly reduced from 1 month to 3-months (P < 0.0001), but not thereafter. Compared with final visits, the changes of mean CFT were not statistically significant in follow up visits (*P* = 0.977 at 1 month and 0.659 at 3-months, respectively; **Table 2**).

Mean GLD was significantly reduced at 1 month, 3-months, and final visits compared with baseline, from 1928.60 ± 995.16 μm at baseline, to 1372.47 ± 795.93 μm at 1 month (P = 0.059), 1170.49 ± 734.69 μm at 3-months (P = 0.002), and 1360.53 ± 830.19 μm at final visits (P = 0.003, **Table 2**). GLD was also significantly reduced from 1 month to 3-months (P < 0.0001), but not thereafter. Compared with final visits, changes of mean GLD were not statistically significant in follow up visits (*P* = 0.977 at 1 month and 0.659 at 3-months, respectively; **Table 2**).

Mean SFCT was significantly reduced at 1 month, 3-months, and final visits compared with baseline, from 65.27 ± 45.81 μm at baseline, to 56.91 ± 39.76 μm at 1 month (P = 0.059), 53.13 ± 38.27 μm at 3-months (P = 0.002), and 51.69 ± 37.97 μm at final visit (P = 0.003, **Table 2**). Compared with 1 month, mean SFCT at each follow up visit was also reduced significantly (*P* = 0.977 at 3-months and 0.659 at final visit, respectively). Compared with 3-months, changes of mean SFCT were not statistically significant in the final visit (*P* = 0.977, **Figure 1** and **Table 2**).

Table 3. Univariate and multivariate regression analysis of the influence on final BCVA of baseline SFCT and other clinical factors of patients with mCNV treated with intravitreal bevacizumab or ranibizumab injections

Factor	Univariate analysis	*P* value	Multivariate analysis	
	Correlation coefficient		Regression coefficient B	*P* value
Age at onset (year)	0.003	0.499		
Male/Female	0.05	0.694		
Baseline BCVA (LogMAR)	0.704	< 0.0001	0.702	< 0.0001
Baseline CFT	0.0003	0.308		
Baseline GLD	2.96×10^{-8}	1		
Baseline SFCT	0.001	0.511		
Baseline axial length	-0.019	0.579		
Subretinal and/or intraretinal fluid at baseline	0.33	0.236		
Staphyloma at baseline	0.19	0.265		
Lacquer cracks at baseline	0.14	0.216		
Tessellated fundus at baseline	0.02	0.931		
Diffuse chorioretinal atrophy at baseline	-0.40	0.074		
Patchy chorioretinal atrophy at baseline	0.07	0.624		
Macular atrophy at baseline	0.08	0.660		
Number of injection	0.009	0.792		
Recurrence	0.317	0.030	0.311	0.002
Follow-up duration	0.003	0.484		

BCVA, best-corrected visual acuity; LogMAR, logarithm of minimal angle resolution; SFCT, subfoveal choroidal thickness; mCNV, myopic choroidal neovascularization; CFT, central foveal thickness; GLD, greatest linear dimension.

SFCT and functional anatomical prognoses

Regarding univariate regression analyses, final BCVA significantly correlated with baseline BCVA (t = 6.479, P < 0.0001) and recurrence (t = 2.249, P = 0.030). In multivariate stepwise regression analyses, baseline BCVA and recurrence also associated significantly with final BCVA (t = 7.129, P < 0.0001, t = 3.239, P = 0.002, respectively; **Table 3**).

In univariate regression analyses, final GLD on SD-OCT was associated with baseline CFT (t = 2.711, P = 0.010), baseline GLD (t = 2.856, P = 0.007), follow up period (t = 2.270, P = 0.028), and recurrence (t = 2.726, P = 0.009). In multivariate stepwise regression analyses, baseline GLD and recurrence associated significantly with final GLD (t = 3.750, P = 0.001, t = 3.643, P = 0.001, respectively; **Table 4**).

Regarding generalized linear model (GLM) analyses, number of injections was associated with recurrence (t = 8.846, P = 0.003; **Table 5**). SFCT showed no significant association with final BCVA, final GLD, or number of injections (all P > 0.05).

Discussion

This present study used SD-OCT to determine the efficacy of anti-VEGF agents, changes of SFCT following anti-VEGF therapy, and its relation to functional and anatomical prognoses in patients with mCNV. Anti-VEGF treatment was shown to be effective to treat mCNV with significant influence on SFCT. However, SFCT was not associated with functional and anatomical prognoses.

Anti-VEGF therapy, which has been more often and widely used in treatment of mCNV in recent years, has been proven to reduce risks of visual acuity loss and increase chances of visual acuity gain [20]. BCVA is the most important functional outcome in the treatment of mCNV. SD-OCT, CFT, and GLD have been considered anatomical indicators to evaluate treatment effects on CNV, including effects on CNV lesions, Subretinal (SRF), intraretinal (IRF), SRF, and retinal edema. Consistent with previous studies [20], anti-VEGF treatment was shown to be effective for treatment of mCNV. Compared with baseline, BCVA improved significantly accompanied by decreased CFT and GLD at one month, three months, and final visit. It

Table 4. Univariate and multivariate regression analysis of the influence on final GLD of baseline SFCT and other clinical factors of patients with mCNV treated with intravitreal bevacizumab or ranibizumab injections

Factor	Univariate analysis		Multivariate analysis	
	Correlation coefficient	*P* value	Regression coefficient B	*P* value
Age at onset (year)	9.357	0.350		
Male/Female	144.96	0.601		
Baseline BCVA (LogMAR)	567.881	0.087		
Baseline CFT	1.892	0.010		
Baseline GLD	0.333	0.007	0.39	0.001
Baseline SFCT	0.320	0.908		
Baseline axial length	1.063	0.988		
Subretinal and/or intraretinal fluid at baseline	752.447	0.214		
Staphyloma at baseline	-450.538	0.220		
Lacquer cracks at baseline	-17.839	0.944		
Tessellated fundus at baseline	-628.725	0.111		
Diffuse chorioretinal atrophy at baseline	-505.929	0.313		
Patchy chorioretinal atrophy at baseline	435.861	0.161		
Macular atrophy at baseline	550.650	0.165		
Number of injection	80.929	0.297		
Recurrence	824.25	0.009	975.71	0.001
Follow-up duration	22.545	0.028		

GLD, greatest linear dimension; SFCT, subfoveal choroidal thickness; mCNV, myopic choroidal neovascularization; BCVA, best-corrected visual acuity; LogMAR, logarithm of minimal angle resolution; CFT, central foveal thickness.

Table 5. Generalized linear model (GLM) analysis of the influence on number of injections of baseline SFCT and other clinical factors of patients with mCNV treated with intravitreal bevacizumab or ranibizumab injections

Factor	Univariate analysis		Multivariate analysis	
	Correlation coefficient	*P* value	Regression coefficient B	*P* value
Age at onset (year)	-0.013	0.083		
Male/Female	-0.186	0.386		
Baseline BCVA (LogMAR)	0.209	0.410		
Baseline CFT	0.000	0.882		
Baseline GLD	0.000	0.586		
Baseline SFCT	0.004	0.036		
Baseline axial length	-0.045	0.416		
Subretinal and/or intraretinal fluid at baseline	-0.168	0.688		
Staphyloma at baseline	0.663	0.089		
Lacquer cracks at baseline	0.094	0.618		
Tessellated fundus at baseline	0.514	0.161		
Diffuse chorioretinal atrophy at baseline	-0.261	0.534		
Patchy chorioretinal atrophy at baseline	0.000	1.000		
Macular atrophy at baseline	0.395	0.124		
Recurrence	0.663	0.001	0.617	0.003
Follow-up duration	0.008	0.266		

SFCT, subfoveal choroidal thickness; mCNV, myopic choroidal neovascularization; BCVA, best-corrected visual acuity; LogMAR, logarithm of minimal angle resolution; CFT, central foveal thickness; GLD, greatest linear dimension.

especially improved much more obviously in the first month after anti-VEGF treatment. However, BCVA at final visit was significantly worse compared with three months and was

correlated almost simultaneously with CFT and GLD increase at final visit. Based on these results, this present study suggests that CFT and GLD reduction is simultaneously associated with visual improvement and has much more significant correlation with visual outcomes in the recovery of mCNV.

VEGF is a survival factor for endothelial cells, increasing microvascular permeability and inducing vasodilation in vessel beds [21]. Both ranibizumab and bevacizumab are pan-isoform inhibitors of VEGF-A, impairing both pathological and physiological actions of VEGF-A. It is important to be aware of the adverse effects of anti-VEGF agents on morphology and vasculature of retinal and choroidal. Some studies have focused on the influence of anti-VEGF agents on SFCT of mCNV eyes [9, 17, 22]. However, results have been contradictory. This current study demonstrated thinner baseline SFCT in both affected eyes with mCNV and fellow unaffected eyes in patients with bilateral pathological myopia, suggesting that thinning SFCT plays a role in the development of mCNV. Further study showed that changes after anti-VEGF injection affect SFCT. Possible explanations for a decrease in SFCT, after anti-VEGF therapy, could be: 1) Induced decreased of nitric oxide, a potent vasodilator, causing vessel vasoconstriction [10]; and 2) Endothelial cell dysfunction and regression of fenestrated capillaries [23]. Moreover, CT decrease could be secondary to a reduction of choriocapillaris endothelial cell fenestrations after VEGF antagonist treatment [14, 24]. For the first time, this present study suggests choroidal thinning as vascular side-effect, result from vasoconstriction after anti-VEGF treatment.

Whether choroidal thickness is a prognostic factor of mCNV after anti-VEGF treatment is less clear and has been much less studied. Although Yang et al. [20] showed that eyes with mCNV showed a significant correlation between final visual and baseline CT, those with myopic CNV have shown no association between visual outcome and choroidal parameters in other studies [9, 18]. The present study consists with the latter, showing no association between visual outcome and SFCT. Thus, association between visual outcome and choroidal thickness may be confounded by the effects of other causes of vision loss, such as chorioretinal atrophy in eyes with myopic CNV. To the best of our knowledge, there have been no other reports concerning association between SFCT and anatomical outcome in patients with mCNV after anti-VEGF therapy. For the first time, this present study showed no association between final GLD, number of injections, and SFCT, suggesting that SFCT is not a functional and anatomical prognostic factor of mCNV.

There were several limitations to this study. First, the retrospective design may have resulted in selection bias. Second, the fellow up period was not long enough to draw a definite conclusion. Third, this study did not calculate choroidal blood flow changes, only choroidal thickness changes to anti-VEGF agents. However, choroidal thickness is a useful surrogate for choroidal perfusion, with changes in choroidal thickness indicating changes in choroidal blood flow. Fourth, although both ranibizumab and bevacizumab are pan-isoform inhibitors of VEGF-A, the use of two different drugs may additionally introduce bias. These limitations indicate that long-term, prospective, and well-designed studies are warranted.

In conclusion, anti-VEGF regimen was proven to be effective for mCNV, probably arousing significant changes in choroidal thickness. However, SFCT was not associated with functional and anatomical prognoses.

Disclosure of conflict of interest

None.

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