Original Research Article

EJO European Journal of Ophthalmology

Optical coherence tomography angiography in myopic choroidal neovascularization after intravitreal ranibizumab

European Journal of Ophthalmology
1–5

DOI: 10.1177/1120672118785495
journals.sagepub.com/home/ejo
SAGE

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Abstract

Purpose: To describe the optical coherence tomography angiography characteristics of myopic patients with choroidal neovascularization secondary to pathologic myopia during ranibizumab therapy.

Methods: Nineteen patients were enrolled in this prospective study (13 females, 6 males, mean age 55.25 ± 9.63 years) for a total of 20 eyes examined (14 right eyes, 6 left eyes). Images were analyzed independently by two examiners.

Results: Mean follow-up was 5.75 ± 1.88 months, with a mean intravitreal injections of 1.90 ± 0.44. Mean best-corrected visual acuity at baseline was 0.39 ± 0.18 logMAR versus 0.26 ± 0.16 logMAR 6 months after treatment. The neovascular area ($Z = -2.091$, $p = 0.037$) was significantly reduced after treatment, whereas vessel density was not ($Z = -1.848$, $p = 0.065$). Moreover, the best-corrected visual acuity was increased ($Z = -3.055$, $p = 0.002$). Neovascular area was significantly correlated with best-corrected visual acuity, at both baseline and follow-up ($p < 0.05$).

Conclusion: Our data suggest that optical coherence tomography angiography is a reproducible non-invasive examination with which to monitor changes in the neovascular area in patients with pathologic myopia treated with ranibizumab.

Keywords

Optical coherence tomography angiography, ranibizumab, choroidal neovascularization, myopia, vessel density

Date received: 20 February 2018; accepted: 7 June 2018

Introduction

Choroidal neovascularization (CNV) has been reported to cause visual loss in 5%–10% of patients affected by pathologic myopia.[1] Pathologic myopia is diagnosed in eyes with a high axial length that manifest degenerative changes of the sclera, choroid, and retina.[2] Fluorescein angiography (FA) is the standard procedure with which to detect early CNV. However, FA is an invasive procedure. Moreover, it is associated with patient discomfort, including anaphylactic reactions, both during and after the examination.[3] In 2006, Garcia-Layana et al.[4] reported that the sensitivity of optical coherence tomography (OCT) B-scans in detecting CNV activity—after a diagnosis of CNV associated with pathologic myopia was established—was about 97%. Nevertheless, in 2013, notwithstanding substantial advances in spectral domain optical coherence tomography (SD-OCT), Leveziel et al.[5] reported that the exudative features of myopic CNV are more evident on FA than on SD-OCT, thereby indicating that FA be performed when new-onset myopic CNV is suspected.

Very recently, optical coherence tomography angiography (OCT-A) has proven to be effective in detecting CNV in patients with pathologic myopia.[6–8] Vascular endothelial growth factor (VEGF) is strongly implicated in simulating CNV growth,[9] and the anti-VEGF ranibizumab improves the course of CNV in pathologic myopia.[10] However, no

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studies have yet evaluated the use of OCT-A during treatment with an anti-VEGF. Consequently, we conducted the present study to assess the vascular changes on OCT-A after an injection of ranibizumab for the treatment of CNV secondary to pathologic myopia.

Methods

Thirty-four eyes from 32 consecutive patients (9 men, 23 women, mean age 55.72 years ± 11.27 SD) with CNV secondary to high myopia admitted to the Eye Clinic of the University Federico II, Naples (Italy) between June 2015 and June 2016. The subjects enrolled were treatment-naïve patients suffering from classical CNV, with an axial length ⩾ 26 mm. The diagnosis of CNV was made based on multimodal imaging, namely multicolor imaging, FA, indocyanine angiography (ICGA), SD-OCT, and OCT-A. Of the 34 eyes, OCT-A images with sufficient image quality for CNV assessment were obtained in 19 patients (13 females, 6 males, mean age 55.25 ± 9.63 years) for a total of 20 eyes (14 right eyes, 6 left eyes). Patients with one or more of the following clinical conditions were excluded from the study: age-related macular degeneration, diabetic retinopathy, a previous diagnosis of glaucoma, optic disk anomaly and congenital eye disorders, low visual acuity (<20/250 due to poor fixation), subretinal fibrosis, media opacities, previous retinal surgery, or laser photocoagulation or hereditary retinal dystrophy. The study was approved by our institutional review board and informed consent was obtained from all subjects before enrollment. All investigations complied with the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). All patients studied underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), using standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts, slit-lamp examination, fundus biomicroscopy, as well as multicolor imaging, FA, ICGA, SD-OCT (Heidelberg Engineering, Heidelberg, Germany) at baseline and during the 6 months of follow-up. All patients also underwent OCT-A (AngioVue, RTVue XR Avanti, Optovue, Inc., Freemont, CA, USA) at baseline and at the end of follow-up. All patients were treated with an average of 1.90 ± 0.44 intravitreal injection (IVT) of ranibizumab (0.5 mg) for 6 months with a 1 + PRN regimen.

OCT-A

We obtained OCT angiography images with the Optovue Angiovue System (Optovue Inc. Fremont, CA, USA), which is based on split-spectrum amplitude decorrelation angiography.[11] To assess the morphology and the flow within the neovascular lesions, we performed a 3 × 3 mm scan of the neovascular area detected with FA. To this aim, we manually segmented 30 μm between the level of Bruch's membrane (inner boundary) and 30 μm underneath the retinal pigment epithelium (RPE) (outer boundary). Using the measuring tool in the AngioVue software, two expert examiners (G.C. and F.A.) independently assessed the manual measurements of the membrane area that correspond to the manually outlined lesion area with the flow draw tool (selected area) and to the total area of the vessels with high flow within the lesion (vessel area). Two vessel and selected area measurements of the same neovascular membrane were obtained by each examiner, at baseline and after IVT during the follow-up. A third investigator (G.D.C.) reassessed the measurements in case of discordance between each independent measurement with more than 10% of variation in the membrane area.

The primary outcome measures were changes in terms of BCVA, and the vessel and selected areas after IVT injection of ranibizumab in myopic CNV. The secondary outcome measures were the correlation between the BCVA and the regression of selected and vessel area. The tertiary outcomes were the average number of injections needed during the follow-up.

Statistical analysis

A statistical analysis was performed with the Statistical Package for Social Sciences (Version 20.0 for Macintosh; SPSS Inc, Chicago, Ill, USA). The Wilcoxon test was used to evaluate the differences in the BCVA and OCT angiography parameters at baseline and after the follow-up. The differences between pre-treatment BCVA and OCT angiography parameters at baseline and between post-treatment BCVA and OCT angiography parameters at follow-up were evaluated with Spearman's correlation. A $p < 0.05$ was considered statistically significant.

Results

Nineteen patients (13 females, 6 males, mean age 55.25 ± 9.63 years) for a total of 20 eyes (14 right eyes, 6 left eyes) were enrolled in this prospective study. Mean axial length was 28.52 ± 2.23. The average follow-up was 5.75 ± 1.88 months, with a mean IVT number of 1.90 ± 0.44. The mean time between the last injection and the last follow-up visit was 3.22 ± 1.12 months. The mean BCVA at baseline was 0.39 ± 0.18 logMAR (66 ± 2 ETDRS letters) and, after follow-up, it was 0.26 ± 0.16 logMAR (74 ± 3 ETDRS letters). At baseline, most multicolor images showed retinal hemorrhage (18 eyes, 90%) with (12 eyes, 60%) or without (6 eyes, 30%) subretinal fluid (Figure 1(a)). FA revealed leakage of the lesion in late phases (Figure 1(c)) and ICGA confirmed the presence of CNV and lacquer cracks in late phases (Figure 1(d)). SD-OCT showed subretinal fluid and perforating vessels respectively in 50% and in 40% of the eyes (Figure 1(e)). Six months after treatment, multicolor imaging, FA, ICGA, and SD-OCT showed resolution of active signs of CNV (Figure 1(g)–(m)).

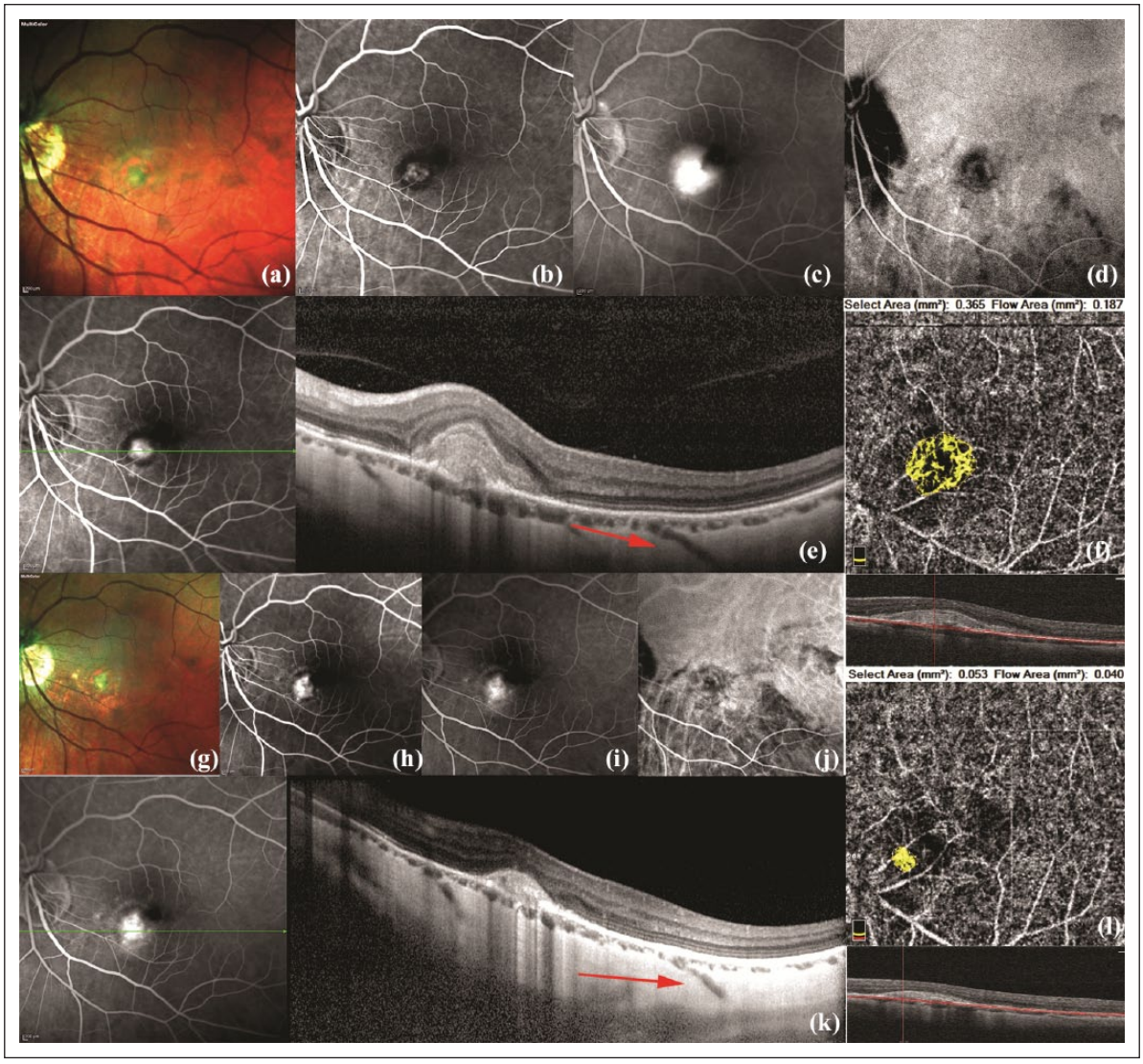

Figure 1. Multimodal imaging of a patient with myopic CNV after anti-VEGF therapy. (a)–(f) Baseline measurements. (a) Multicolor image showing, nasally to the fovea, a small retinal hemorrhage. (b) Fluorescein angiography showing hyperfluorescence of the CNV in the early phases, (c) leakage in late phases, (d) ICGA confirming the presence of myopic CNV and lacquer cracks in the late phases, (e) SD-OCT showing the typical aspect of type 2 CNV, with visible perforating vessels (red arrow), (f) OCT-A (3 × 3) showing an interlacing vascular network at the level of the choriocapillaris segmentation. (g)–(n) After anti-VEGF treatment. (g) MC showing the resolution of the retinal hemorrhage and the fibrosis of the neovascular lesion (h). Fluorescein angiography revealing the hyperfluorescence of the CNV in the early phases (i) with a reduction of leakage in the late phases (l). ICGA showing lacquer cracks in the late phases (m). SD-OCT showing resolution of CNV activity, with persistence of perforating vessels (red arrow). (n) OCT-A (3 × 3) revealing a tangled vascular network at the choriocapillaris segmentation, with a reduction of the neovascular area and the vessel density after treatment.

Both the BCVA ($Z = -3.055$, $p = 0.002$) and the neovascular area ($Z = -2.091$, $p = 0.037$) were significantly reduced after 6 months of treatment (Figure 1(n)), whereas vessel density was not ($Z = -1.848$, $p = 0.065$) (Table 1). Notably, neovascular areas were significantly correlated with the BCVA at both baseline and follow-up ($p < 0.05$), whereas there was no correlation between post-treatment vessel density and BCVA (Table 2). Finally, OCT-A images showed a switch from an interlacing network pattern to a tangled network pattern in 17 eyes (85%).

Discussion

To our knowledge, this is the first study to use OCT-A to evaluate vascular changes of myopic CNV after IVT of ranibizumab. FA is currently the standard procedure with which to monitor changes in the CNV area in pathological myopia.[12] The combination of SD-OCT and FA has been shown to be more sensitive than FA or SD-OCT alone.[13] Recently, Myiata et al.[6] reported that OCT-A can be used as an alternative to conventional FA for the detection of CNV in pathologic myopia. Their results indicated that OCT-A

Table 1. Characteristics of the study population at baseline and 6 months after treatment.

	Patients (n = 19) Baseline	Patients (n = 19) Follow-up	p-value
Eyes, n	20		
Female, n	13 (68.4%)		
Age, years	65.05 ± 11.54		
Right eyes, n	14 (70%)		
Perforating vessels, n	8 (40%)		
Refractive error, diopters	−10.7 ± 2.41		
Follow-up, months	5.75 ± 1.88		
IVT, n	1.90 ± 0.44		
BCVA baseline, logMar	0.39 ± 0.18	0.26 ± 0.16	0.002
Neovascular area	0.803 ± 1.025	0.502 ± 0.588	0.037
Vessel density	0.483 ± 0.588	0.328 ± 0.362	0.065

IVT: intravitreal injection; BCVA: best-corrected visual acuity.

Table 2. Correlationbetween OCT angiography parameters and BCVA at baseline and at follow-up.

	BCVA baseline		BCVA follow-up	
	Z value	p-value	Z value	p-value
Baseline				
Neovascular area	0.510	0.022	–	–
Vessel density	0.483	0.031	–	–
Follow-up				
Neovascular area	–	–	0.444	0.049
Vessel density	–	–	0.413	0.070

BCVA: best-corrected visual acuity.

can detect most myopic CNVs, and FA can be used if high-quality images are required. Querques et al.[7] described the structural features of myopic CNV on OCT-A. They proposed two types of myopic CNV: one due to an interlacing network and other due to a tangled network. The interlacing network is characterized by dense vascular hyper-intensity, with a well-circumscribed appearance on OCT-A. This appearance is often associated with neovascular activity on conventional imaging, namely FA and OCT B-scan. The tangled network is defined by a loosely laced appearance on OCT-A. This pattern can be associated with the absence of neovascular activity on conventional imaging, namely FA and OCT B-scan. Subsequently, Querques et al.[14] classified the morphologic features of myopic CNV as follows: shape, core, margin, and appearance

FA confirmed active leakage in all CNVs areas detected by OCT-A. Moreover, OCT-A revealed an interlacing network before treatment and a tangled network after treatment. OCT-A also showed a statistically significant reduction of the neovascular area after treatment (Figure 1(f) and (n)), whereas the reduction of vessel density was not significant. Furthermore, the neovascular area was significantly correlated with the BCVA at both baseline and follow-up. These results suggest that OCT-A, particularly neovascular area, when available, may be a viable alternative to invasive FA for the detection of myopic CNV and its follow-up after treatment. Moreover, unlike SD-OCT, OCT-A reveals different CNV patterns that are correlated with neovascular activity.

This study has several limitations, namely, the relatively low number of patients enrolled, the difficulty in obtaining reliable images from patients, distorted images in eyes with unstable fixation due to myopic CNV and image artifacts.

In conclusion, OCT-A is a useful tool with which to detect CNV secondary to pathologic myopia and to monitor vascular changes after anti-VEGF treatment. Larger studies with a longer follow-up are needed to verify these findings.

Acknowledgements

The authors thank Jean Ann Gilder (Scientific Communication srl., Naples, Italy) for writing assistance. These data were partially reported at the "17th Euretina Congress," Barcelona 7–10 September 2017.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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