American Journal of Ophthalmology Case Reports 25 (2022) 101267

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

State of the art spatial visualization of the response of neovascularisation to anti-vascular endothelial growth factor therapy

Mali Okada [a,b], Catherine A. Egan [a,c], Tjebo FC. Heeren [a,c,d], Philippe Valmaggia [e,f], Adnan Tufail [a,c], Peter M. Maloca [a,e,f,*]

[a] Moorfields Eye Hospital NHS Foundation Trust, London, EC1V 2PD, United Kingdom
[b] Royal Victorian Eye and Ear Hospital, 32 Gisborne St, East Melbourne, VIC, 3002, Australia
[c] Institute of Ophthalmology, University College London, 11-43 Bath St, Greater, London, EC1V 9EL, United Kingdom
[d] Department of Ophthalmology, University of Bonn, 53127, Bonn, Germany
[e] Department of Ophthalmology, University of Basel, Mittlere Str. 91, 4056, Basel, Switzerland
[f] Institute of Molecular and Clinical Ophthalmology Basel (IOB), Mittlere Strasse 91, Basel, 4056, Switzerland

ARTICLE INFO

Keywords:
Optical coherence tomography angiography
Volume-rendering
Macular telangiectasia
Retina
Neovascularization
Anti-VEGF

ABSTRACT

Purpose: To visualize the mode of action of anti-vascular endothelial growth factor (*anti*-VEGFs) therapy on retinal neovascularization (RNV) in a patient with macular telangiectasia (MacTel) type 2 using a detailed three-dimensional data environment.

Observation: A 60-year-old man presented with visual acuity loss and was diagnosed with MacTel type 2. Fluorescein angiography was not possible for safety reasons because of a history of severe reaction to fluorescein dye at his referring hospital. Optical coherence tomography angiography (OCTA) imaging revealed new retinal neovascular membranes (RNV) in the macula of both eyes. A marked reduction in the size of the RNV in both eyes was evident on volume-rendered three-dimensional OCTA retinal imaging after the first *anti*-VEGF injection.

Conclusion and importance: The ability to directly observe the effect of *anti*-VEGF injections on a RNV using three-dimensional OCTA was successfully demonstrated. This can be useful in patients with previous allergic and potentially lethal complications to fluorescein. In addition, enhanced three-dimensional spatial display of RNV leads to a greater understanding of the perfusion profile and the anatomical changes that occur in ocular neovascularization relative to surrounding tissue. This has the potential to provide insight into the pathobiology of angiogenesis.

1. Introduction

Angiogenesis plays a key role in both health and disease and has been recognized in the development of cancers as far back as 1865.[1,2] Treatment with anti-vascular endothelial growth factor (*anti*-VEGF) intravitreal injections have revolutionized treatment for several common and potentially blinding vascular diseases of the eye including neovascular age related macular degeneration (AMD) and diabetic macular edema (DME).[3–5]

The rapid uptake of *anti*-VEGF therapy in ophthalmology has been partially enabled by the concurrent advances made in ophthalmic imaging technology. Optical coherence tomography (OCT) in particular, has been instrumental in allowing repeated non-invasive high-resolution cross-sectional imaging of the eye.[6–8] Recent developments have taken OCT technology one step further, with optical coherence tomography angiography (OCTA) now using motion-contrast OCT scans to produce detailed volumetric maps of retinal and choroidal microvasculature.[9,10]

Here, we present an improved in-depth three-dimensional (3D) representation of the effect of *anti*-VEGF therapy on a retinal neovascular lesion in a patient with macular telangiectasia (MacTel) type 2, demonstrating the potential of this technology to identify the spatial effect of blood vessel targeted therapy.

2. Case report/Findings

A 60-year-old man was referred to the medical retinal clinic at Moorfields Eye Hospital, London, in 2013 with gradual onset of reading difficulty in both eyes. Visual acuity was 20/30 in the right eye and 20/

* Corresponding author. Institute of Molecular and Clinical Ophthalmology Basel (IOB), 4031, Basel, Switzerland.
E-mail address: peter.maloca@iob.ch (P.M. Maloca).

https://doi.org/10.1016/j.ajoc.2022.101267
Received 3 March 2021; Received in revised form 3 January 2022; Accepted 10 January 2022
Available online 20 January 2022

20 in the left eye. He was diagnosed with MacTel type 2, a progressive neurodegenerative disease of the macula with characteristic vascular alterations,[11] based on typical findings on fundoscopic examination and multimodal non-invasive retinal imaging (Fig. 1). Fluorescein angiography was not performed due to a history of severe allergic reaction to the fluorescein dye at his referring hospital, with body rash and angioedema of the face. However, there was no evidence at baseline of retinal neovascularization in either eye on clinical examination or on OCT imaging. No treatment is currently approved for the non-proliferative stage of MacTel type 2 and he was advised to monitor his vision.

Three years later, he presented to the emergency department with new onset symptoms of a central scotoma in his right eye for 2 months and distortion in his left eye for the last 2–3 weeks. Visual acuity had deteriorated to 20/200 in the right and 20/60 in the left. Optical coherence tomography imaging revealed new retinal neovascularization (RNV) in the macula of both eyes secondary to MacTel type 2. He was commenced on monthly ranibizumab 0.5mg intravitreal injections, with a protocol of three injections given monthly. After three injections, visual acuity in the left eye improved to 20/40 but remained unchanged in the right eye due to extensive neurosensory atrophy and scarring. A marked reduction in the size of the RNV in both eyes was evident on retinal imaging after the first injection.

2.1. Response of neovascular lesion on three-dimensional imaging

The dramatic response of the RNV to *anti*-VEGF therapy in this patient is clearly visualized on non-invasive OCTA imaging. Before *anti*-VEGF therapy, OCTA shows an abnormal retinal neovascularization network. After *anti*-VEGF therapy, there is pruning of this

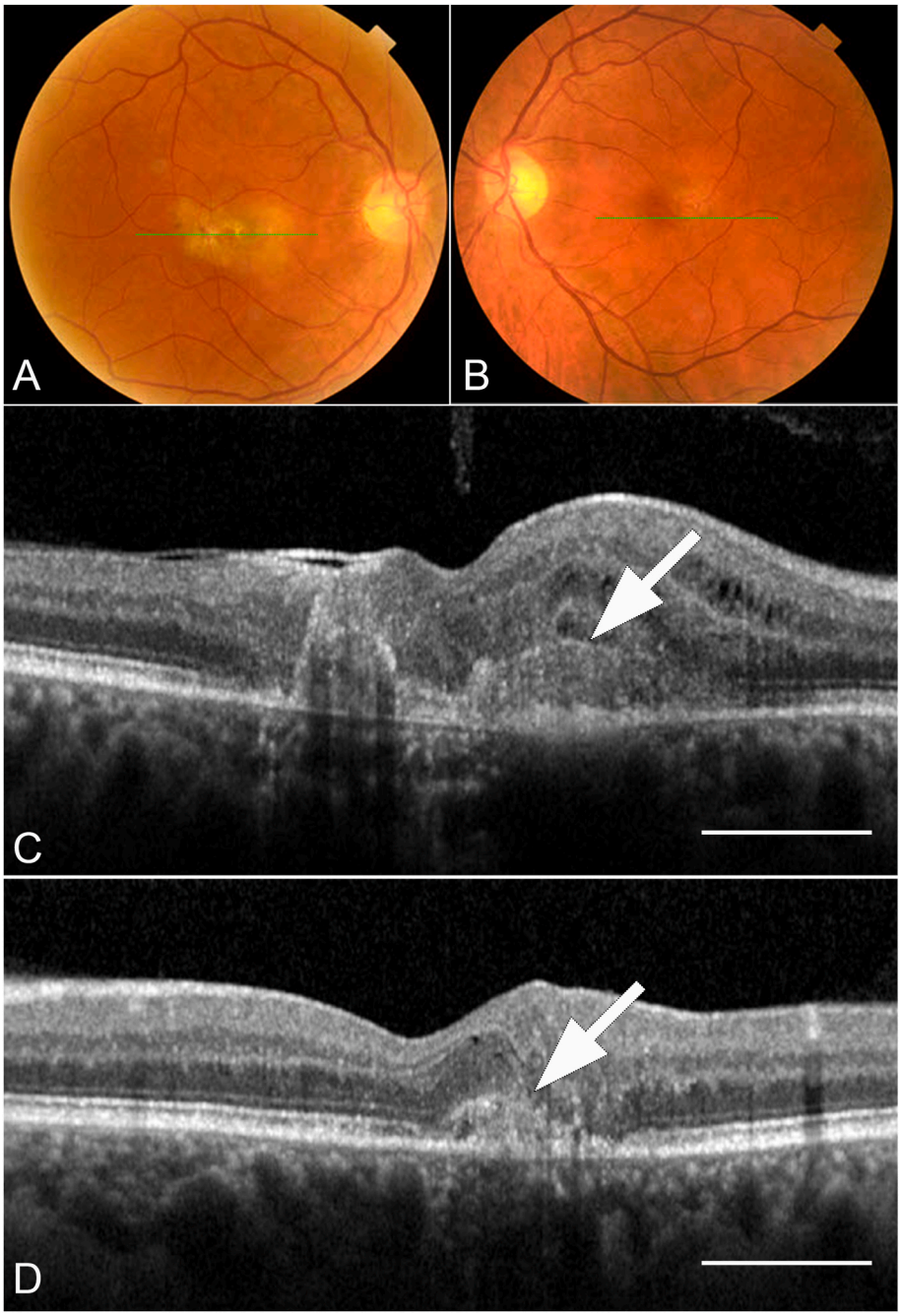

Fig. 1. Standard retina imaging in macular telangiectasia type 2. Color fundus photos of a 60-year-old male patient with macular telangiectasia type 2 (A, right eye, B, left eye). Lines denotes level of the cross-sectional optical coherence tomography scans below. (C) Cross-sectional OCT scan of the same eye as in (A) with large hyper-reflective retinal lesion consistent with neovascular membrane (arrow). (D) OCT scan of the left macula as depicted in (B) with similar but smaller lesion. Line, 1 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

neovascularization leaving a residual central vascular core and a three-dimensional void of reduced signal intensity in the space previously occupied by the frond. However, there is no apparent change to the surrounding normal retinal vascular architecture.

3. Material and methods

Macula OCTA scans were obtained with Zeiss Cirrus HD-OCT Model 5000 with AngioPlex (Review software 9.0.0.281, Carl Zeiss Meditec, Jena, Germany) using a 3mm × 3mm (245 × 245 pixel) scan protocol. Currently, scans of the right eye were visualized to demonstrate the effect of *anti*-VEGFs: at baseline and at three months after the third intravitreal injection of ranibizumab (Fig. 1.). En face data were exported from the OCT system and retinal vessels segmented and visualized (AMIRA software, version 6.0.1, FEI, Thermo Fisher Scientific, Waltham, Massachusetts, United States). To compare the change over time, volume scans were aligned, overlaid and reconstructed into a volume rendered three-dimensional (3D) OCTA video montage that can be found as Supplementary video related to this article.

4. Discussion

Here we demonstrate the response of a pathological RNV to *anti*-VEGF therapy with three-dimensional high-resolution angiography rendered from non-invasive OCTA imaging. This case highlights the unprecedented microscopic detail and access now possible with modern ophthalmic image display techniques as a means to understanding the biology of human vasculature in vivo. This was particularly useful since

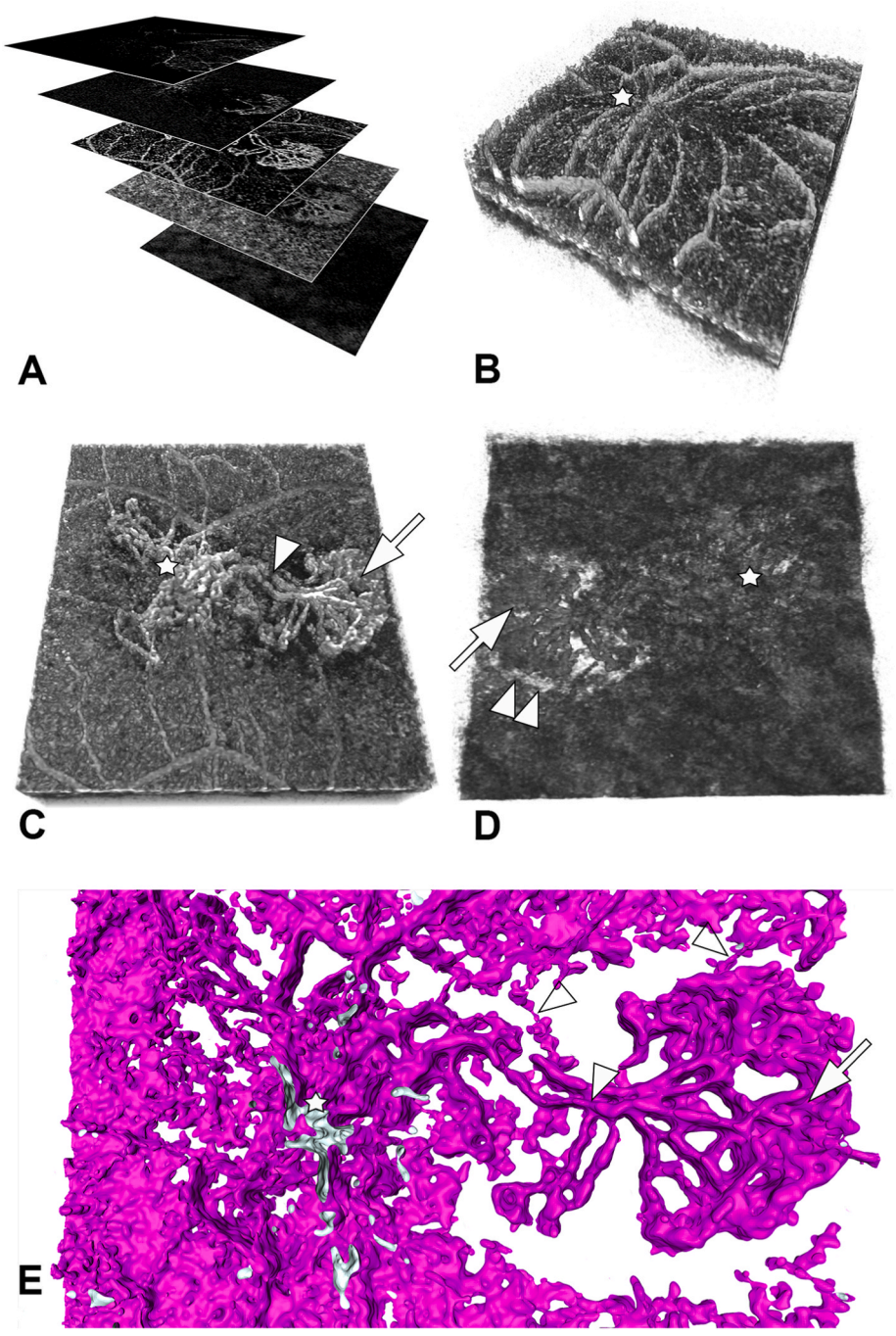

Fig. 2. Demonstrating workflow of volume-rendered 3D OCT angiography. (A) Images taken of the macula are exported as en face images. (B) All images were then stacked into a volume and rendered for a three-dimensional data representation. Thereby, it can be observed that the vessels are typically directed to an assumed epicenter (marked as star). (C) Spatial view of inside the 3D OCTA rendering. The epicenter of the RNV (star) is shown from which a vascular stalk (white arrow head) is grown out and supplies a flower-shaped retinal neovascularization (arrow). (D) Advanced rear 3D OCTA view of RNV allows even for an exploration of the posterior surface of the RNV (arrow), which is not possible in the standard en face OCTA method. In additional, a signal weak halo (double arrow heads) around the RNV is uncovered. (E) Segmentation of the OCTA vessels shows the epicenter (star), the vascular stalk (white arrow head) and the RNV (arrow), but also presumed vascular side connections (open arrow heads).

the neovascularization extent and diagnosis could be made and the patient had an additionally aggravating life-threatening allergy to fluorescein. Although the effect of *anti*-VEGF therapy on choroidal neovascular membranes has previously been described using two-dimensional (2D) OCTA,[12,13] to our knowledge, this case is unique as it is the first 3D reconstruction of a rare retinal not choroidal derived neovascular process and also demonstrates in detail the structural architecture of regression with *anti*-VEGF therapy.

Optical coherence tomography angiography relies on the principle of motion-detection to produce images of the vasculature.[9,14] In contrast to normal fluorescein angiography, no dye injection is required, rendering it a safe, fast and reproducible imaging modality. Total acquisition time is typically seconds compared to the 8–10 minutes required for fluorescein angiography.[10] As it is an office-based test, it can be performed at every patient visit and is therefore useful not only as a diagnostic tool but also for disease and therapeutic monitoring.

A significant advantage of OCTA is also its ability to provide high-resolution depth-resolved structural and perfusion data. Just as advancements have been made in radiology from plain X-rays to 3D reconstructed computed tomography imaging, this technology has the capability to demonstrate the close relationship of the microvascular architecture as it exists in vivo, but remarkably, now down to the micron level. Traditionally, in angiography performed for other body systems, such as for cardiovascular or cerebrovascular imaging, the injected contrast is limited to only delineating flow in relatively larger vessels; needing instead to rely on surrogate signals such as leakage to indicate the integrity of small vessel structures.[15] In contrast, the ophthalmic imaging here involves non-invasive dye-free direct visualization of detailed microscopic capillary networks. Indeed, the RNV demonstrated in this case is encompassed within a scan less than 3 mm in dimension and where calculation of lesion volume in microns is possible (Fig. 2).

The spatial resolution of OCTA therefore lends itself to the study of neovascularization and disorders of perfusion. Recently, OCTA has helped to identify a new subtype of choroidal neovascularization (CNV) in AMD that was not previously visible on traditional fluorescein angiography or structural OCT.[16,17] This finding of 'quiescent' CNV has now also been observed in other ocular choroidal neovascular diseases.[18]

Furthermore, although the introduction of *anti*-VEGF has led to a paradigm shift in the treatment of ocular neovascular diseases, there is still much that remains unknown.[3] In particular, not all forms of neovascular lesions respond to treatment or do so suboptimally.[19] Although our case is that of RNV, choroidal neovascular membrane (CNVM) is more common and is typically associated with neovascular AMD. In AMD, treatment with *anti*-VEGF can demonstrate partial regression of the choroidal lesion, but complete regression of the CNVM is rare. Maintenance therapy with repeated injections is therefore usually required but despite this, some may have very poor response. Attempts to look for clinical or genetic factors that may predict the response have been made but results have been inconsistent.[20]

It has been proposed that the poor response in chronic CNVM from AMD may be due to the differing dependency of VEGF as a driving factor over time.[21] With vessel maturation, extracellular matrix is laid down and may provide survival signals that reduce the endothelial cell's dependency on VEGF. This process of maturation may occur more quickly in AMD as compared to other causes of CNVM such as myopia. Our case of RNV in MacTel 2 demonstrates rapid response to *anti*-VEGF and significant pruning of the abnormal vessels down to its vascular core after just 3 injection, highlighting the differences in vessel response with this aetiology.

This variability in treatment efficacy is perhaps even more striking in oncology. Several theories have been proposed for the cause of treatment failure with *anti*-VEGF in cancer therapy, including the possibility of 'vascular normalization' or the heterogeneity of tumor blood vessels.[22] The exact mechanism however of VEGF action on tumor vessels is still debated. Clearly, more needs to be known about the pathophysiologic response of neovascular lesions to different *anti*-VEGF therapies. Detailed functional imaging such as this, which reveals features at the capillary level, may provide greater insight into the mechanism of vascular remodeling in disease and has the potential for cross-translation from ophthalmology to other domains.

5. Conclusions

Future technological advancement is likely to see further growth in this field as novel imaging techniques help clinicians and scientists to reassess, and redefine in high resolution, pathologies that were previously inaccessible to us before. Direct visualization of the effects of treatment on pathological vessels, as seen in our case, is an engaging format and a more realistic 3D representation of the tissue. Not only does this have obvious clinical and scientific value, but also has the added benefits of engaging the patients receiving the treatment. The potential to non-invasively image in the office systemic treatments targeting 'revascularization' could also be explored, heralding a fundamental rethink of the way we view therapy outcomes in the future.

Patient consent

Written informed consent to publish the case report was obtained.

Funding

The study was supported by the National Institute for Health Research (NIHR) and Biomedical Research Centre at Moorfields Eye Hospital and the University College London Institute of Ophthalmology.

AT receives a proportion of funding from the National Institute for Health Research (NIHR) and Biomedical Research Centre at Moorfields Eye Hospital and the University College London Institute of Ophthalmology. PMM is a consultant at Zeiss Forum and holds intellectual properties for machine learning at MIMO AG, and VisionAI, Switzerland. The following authors have no financial disclosures: MO, CAE, TFCH, PV.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

AT receives a proportion of funding from the National Institute for Health Research (NIHR) and Biomedical Research Centre at Moorfields Eye Hospital and the University College London Institute of Ophthalmology. PMM is a consultant at Zeiss Forum and holds intellectual properties for machine learning at MIMO AG, and VisionAI, Switzerland. The following authors have no financial disclosures: MO, CAE, TFCH.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2022.101267.

References

1. Ribatti Domenico. *History of Research on Tumor Angiogenesis*. Netherlands: Springer Science & Business Media; 2009.
2. Ferrara N. VEGF and the quest for tumour angiogenesis factors. *Nat Rev Cancer*. 2002;2(10):795–803.

3. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov*. 2016;15(6):385–403.
4. Kwong TQ, Mohamed M. Anti-vascular endothelial growth factor therapies in ophthalmology: current use, controversies and the future. *Br J Clin Pharmacol*. 2014; 78(4):699–706.
5. Pozarowska D, Pozarowski P. The era of anti-vascular endothelial growth factor (VEGF) drugs in ophthalmology, VEGF and anti-VEGF therapy. *Cent-Eur J Immunol*. 2016;41(3):311–316.
6. Adhi M, Duker JS. Optical coherence tomography–current and future applications. *Curr Opin Ophthalmol*. 2013;24(3):213–221.
7. Ripandelli G, Coppe AM, Capaldo A, Stirpe M. Optical coherence tomography. *Semin Ophthalmol*. 1998;13(4):199–202.
8. Kostanyan T, Wollstein G, Schuman JS. New developments in optical coherence tomography. *Curr Opin Ophthalmol*. 2015;26(2):110–115.
9. Gao SS, Jia Y, Zhang M, et al. Optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT27–36.
10. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitr*. 2015;1(1):5.
11. Charbel Issa P, Gillies MC, Chew EY, et al. Macular telangiectasia type 2. *Prog Retin Eye Res*. 2013;34:49–77.
12. Spaide RF. Optical coherence tomography angiography signs of vascular abnormalization with antiangiogenic therapy for choroidal neovascularization. *Am J Ophthalmol*. 2015;160(1):6–16.
13. Lumbroso B, Rispoli M, Savastano MC. Longitudinal optical coherence tomography-angiography study of type 2 naive choroidal neovascularization early response after treatment. *Retina Phila Pa*. 2015;35(11):2242–2251.
14. Spaide RF, Klancnik Jr JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015;133(1):45–50.
15. O'Connor JPB, Tofts PS, Miles KA, Parkes LM, Thompson G, Jackson A. Dynamic contrast-enhanced imaging techniques: CT and MRI. *Br J Radiol*. 2011;84(2): S112–S120.
16. Choi W, Moult EM, Waheed NK, et al. Ultrahigh-speed, swept-source optical coherence tomography angiography in nonexudative age-related macular degeneration with geographic atrophy. *Ophthalmology*. 2015;122(12):2532–2544.
17. Al-Sheikh M, Iafe NA, Phasukkijwatana N, Sadda SR, Sarraf D. Biomarkers OF neovascular activity IN age-related macular degeneration using OCT angiography, Retina [Internet] 9000;Publish Ahead of Print. Available from: http://journals.lww.com/retinajournal/Fulltext/publishahead/BIOMARKERS_OF_NEOVASCULAR_ACTIVITY_IN_AGE_RELATED.96938.aspx.
18. Carnevali A, Capuano V, Sacconi R, et al. Optical coherence tomography angiography of treatment-naïve quiescent choroidal neovascularization in pachychoroid neovasculopathy. Ophthalmol Retina [Internet] [cited 2017 Jun 7]; Available from: https://doi.org/10.1016/j.oret.2017.01.003.
19. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Dev Ther*. 2016;10: 1857–1867.
20. Finger RP, Wickremasinghe SS, Baird PN, Guymer RH. Predictors of anti-VEGF treatment response in neovascular age-related macular degeneration. *Surv Ophthalmol*. 2014;59(1):1–18.
21. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res*. 2015;49:67–81.
22. Sitohy B, Nagy JA, Dvorak HF. Anti-VEGF/VEGFR therapy for cancer: reassessing the target. *Cancer Res*. 2012;72(8):1909–1914.