Original Article

Response to anti-vascular endothelial growth factor of abnormal retinal vascular net in para foveal telangiectasia group II images on optical coherence tomography-angiography

Ketan Saoji, Avinash Pathengay, Jay Chhablani, Bhavik Panchal, Shreyansh Doshi, Merlin Saldanha

Purpose: To identify optical coherence tomography-angiography (OCT-A) findings to predict treatment response during anti-vascular endothelial growth factor (VEGF) therapy in eyes with para foveal telangiectasia (PFT) group II. **Methods:** In this retrospective series, Twelve eyes of seven patients diagnosed with PFT group II without evidence of sub-retinal neovascular membrane (SRNVM) clinically or on spectral domain-OCT (SD-OCT) were included. All patients underwent OCT-A on the Topcon DRI OCT Triton® with 4.5 mm macula scans. The patients with abnormal vascular nets were further classified into type A and B nets and administered intravitreal anti-VEGF therapy. Visual acuity and size of type A and B nets were evaluated pre- and post-injection. Paired *t*-test and intraclass correlation were used to analyse data. **Results:** Patients with type A net showed significant improvement in visual acuity (logMAR 0.38, $P = 0.0047$). The size of type A net showed statistically significant decrease ($P = 0.0008$) on 6 month follow up. Type B net did not show statistically significant difference in visual acuity or size following anti-VEGF therapy. **Conclusion:** OCT-A plays an important role in early detection of possible neovascular nets (type A), in the absence of obvious SRNVM. Treatment decisions based on OCT-A may be helpful to achieve better visual outcome.

Key words: Avastin, non-proliferative para foveal telangiectasia, optical coherence tomography-angiography

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Patients with para foveal telangiectasia (PFT) usually present with gradual decrease in vision secondary to foveal atrophy or secondary neovascularisation.[1] Gass and Blodi[2] showed about 14% of patients in their case series presented with neovascularisation. Patients with neovascularisation in PFT are associated with poor visual outcome with 80% eyes being worse than 20/200.[3] Anti-vascular endothelial growth factor (VEGF) therapy in PFT has been observed to have variable results of visual improvement especially in non-proliferative stage.[4,5] The reason for this variable response could not be completely explained based on fundus fluorescein angiography (FFA) or spectral domain-ocular coherence tomography (SD-OCT).

Optical coherence tomography-angiography (OCT-A) helps study segmentation of intraretinal vascular network and vascular abnormality. OCT-A features reported in PFT include dilated perifoveal vessels, elongated and widely spaced capillary segments, dragging of vessels and encroachment of foveal avascular zone (FAZ).[6–8] However, presently there is a gap in understanding these OCT-A features to make treatment decisions or assess treatment response. We attempt to fill this gap by sub-classifying the abnormal vascular nets based on OCT-A features into type A and B and assessing treatment response to anti-VEGF in terms of visual acuity change.

Methods

This retrospective study was conducted at tertiary eye institute. The study was cleared by the Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. An informed consent was taken from all patients for the diagnostic and therapeutic procedure.

Twelve eyes of seven patients diagnosed as PFT type IIA with no evidence of sub-retinal neovascular membrane (SRNVM) clinically or on SD-OCT were included in the study. All data were accessible through electronic medical records stored in institute server with each patient's UHID. Exclusion criteria included eyes with presence of SRNVM on clinical examination (clinically visible membrane or sub-retinal haemorrhage or intraretinal haemorrhage) or on SD-OCT (presence of localised retinal thickening or sub-retinal fluid or pigment epithelial detachment) or presence of any other ocular co-morbidity such as diabetic retinopathy.

All patients underwent comprehensive ophthalmic examination. Best-corrected visual acuity was measured on the Snellen's chart and converted to logMAR equivalent. OCT-A on the Topcon DRI OCT Triton® with 4.5 mm macula scans was performed for all patients. Patients were evaluated for the presence of abnormal vascular nets on OCT-A. Abnormal vascular nets were defined by presence of any of the following features – terminal dilated bulbs on perifoveal vessels, dilated

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perifoveal vessels, vessels distorting FAZ, bunching of vessels and vessels in outer retina [Fig. 1]. The abnormal vascular nets seen on OCT-A were sub-classified into two types, A and B. Type A net was defined by presence of any of the following features; vascular net in outer retina [Fig. 1d], bunching up of vessels [Fig. 1c], vessels discontinuous with surrounding perifoveal vessels in any of the segmentation slabs on OCT-A else they were classified as type B. Two masked observers graded the images into two types. In case of discrepancy, consensus was taken after discussion. The patients with abnormal vascular nets (both type A and B) were advised intravitreal anti-VEGF injections and response assessed.

All patients with abnormal vascular nets received intravitreal injection of 1.25 mg (0.05 ml) of bevacizumab (Avastin, Roche, Grenzach, Germany) was performed in operating room with aseptic precautions. The off-label use of the drug and its potential risks were discussed with all patients and informed consent was obtained. The patients were treated with a loading dose of three injections 1 month apart and followed by pro re nata (PRN) dosing.

Visual acuity change was considered significant if more than two lines change from baseline visual acuity was noted. Visual acuity change of less than two lines was considered stable. The size of the type A and B net was measured with the help of area measuring tool of the IMAGEnet®5 software provided with the Topcon DRI OCT Triton®. The nets were outlined manually by two observers and software calculated the area of the net. Intraclass correlation (ICC) calculated by the SPSS version 19 was used to assess consistency of measurements. The area of the net was calculated for each eye before initiating therapy and again on 6 monthly follow up. The nets were also evaluated for any change in morphological features or type of net post-anti-VEGF injections.

Statistical analysis

Snellen's visual acuity was converted into logMAR for statistical analysis. Paired *t*-test was applied to assess statistical significance of observed improvement in visual acuity and also the change in the size of type A and B net before initiating treatment and on 6 monthly follow up. Statistical calculations were performed using the GraphPad website.

Results

The mean age of presentation was 58.5 years (range 42–70 years). Twelve eyes of seven patients were included in the study, three male and four female patients. Seven out of 12 eyes showed type A (neovascular) net and remaining 5 showed type B (telengectatic) net. The average intravitreal bevacizumab injection per eye was 4 ± 0.73 injections. All patients got minimum of three injections following which re-treatment was based on visual acuity improvement. They were kept under follow up on stabilisation of visual acuity.

Six out of seven eyes with type A net showed significant improvement (minimum of two line improvement from baseline) with an average improvement of 0.38 logMAR units from baseline (P = 0.0047, 95% confidence interval 0.2033–0.5887). One eye (eye 12) from type A net subset had stable vision. He had 0.08 logMAR improvement in vision but failed to meet the study defined criteria of significant improvement. All patients belonging to type B net showed

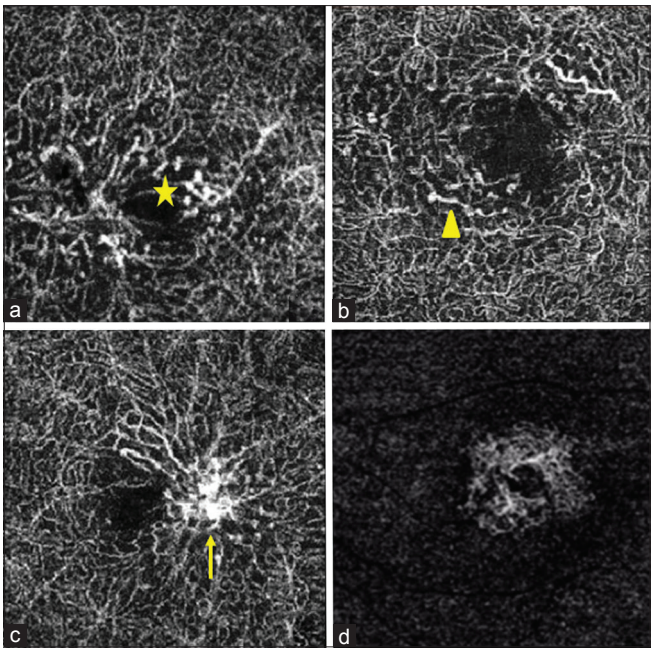

Figure 1: (a) Shows terminal dilated bulbs on perifoveal vessels (star); (b) shows dilated perifoveal vessels (arrow head) with distorted foveal avascular zone; (c) shows bunching up of vessels (arrow) and appear discontinuous with perifoveal vessels; (d) shows vascular net in outer retina

no significant change in visual acuity from baseline. The patients with type A net showed a decrease in size of the net at 6 months compared to pre-treatment size [Fig. 2]. The average decrease in the size of type A net was 50.39% from baseline (P = 0.0008, 95% confidence interval 30.82–70.262). The ICC between two masked observers for measurements of the net on OCT-A scan was 0.89. Type B net did not show change on treatment [Fig. 3]. There was no change in the morphological features of type A or B net pre- and post-treatment.

Type A or B net features can be present on multiple slabs in a single patient and not limited to a single slab on OCT-A. Type A net was commonly observed at the level of outer retina slab on OCT-A (six eyes) followed by deep superficial retina (three eyes), superficial retina (two eyes) and choriocapillaris (one eye). Type B net was seen most commonly in deep superficial retina (five eyes) and superficial retina (two eyes), with no involvement of outer retina.

Three out of seven eyes with type A net had hyperpigmentation on fundus evaluation. All three eyes had hyperpigmentation corresponding to the site of presence of the net on OCT-A. Similarly, four out of five eyes with type B net had hyperpigmentation which also showed correspondence between site of the net and hyperpigmentation. However, type A and B pattern of vascular net and the level of hyperpigmentation in the layer of retina did not always correspond.

Discussion

The use of anti-VEGF in non-proliferative stage of PFT is still controversial. There are reports showing transient improvement in visual acuity in patients before the severe atrophic changes set in[9] as well as reports documenting no improvement in

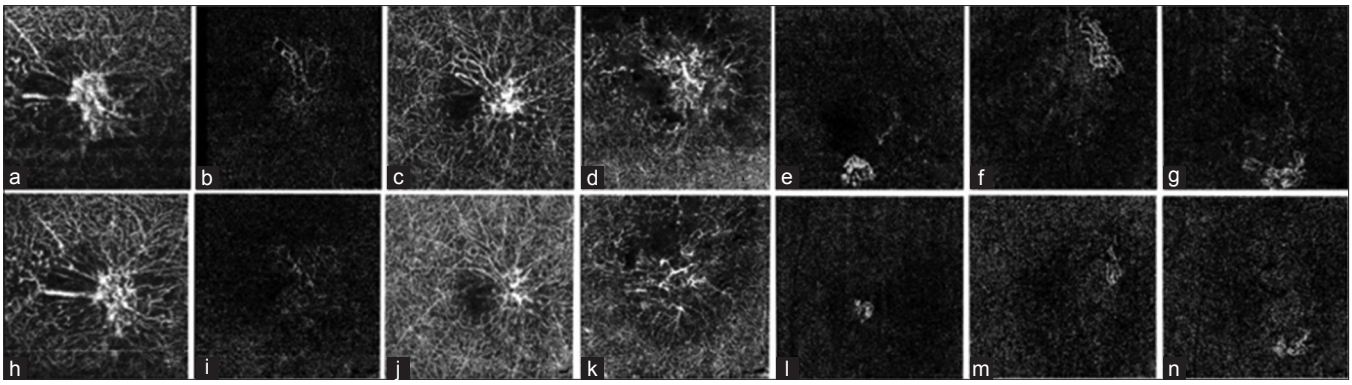

Figure 2: Composite of all patients with type A net. (a–g) Show type A net pre-treatment and (h–n) show same nets post-treatment with intravitreal anti-VEGF injections

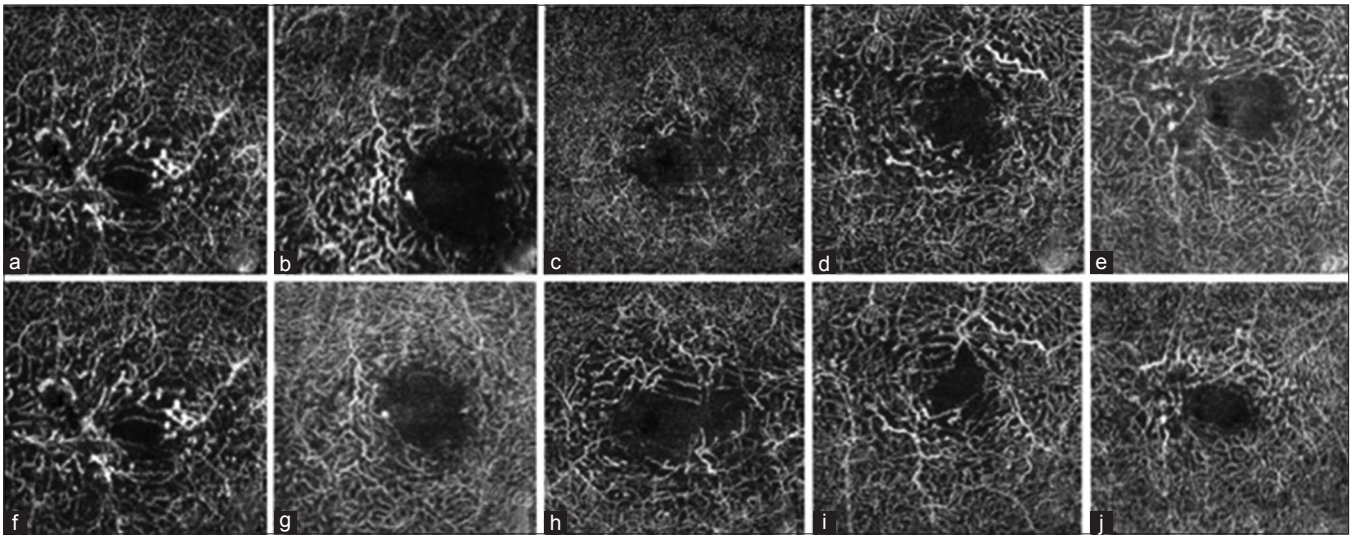

Figure 3: Composite of all patients with type B net. (a–e) Show type B net pre-treatment and (f–j) show same nets post-treatment with intravitreal anti-VEGF injections

visual acuity in spite of repeated injections.[10] This dilemma is further compounded with reports explaining a possible neuroprotective role of physiological VEGF.[11,12] Thus, treating all patients with non-proliferative PFT could be detrimental for the patient. Charbel *et al*.[4] studied anti-VEGF response in non-proliferative PFT with the help of FFA and OCT. They observed a decrease in leakage on FFA and macular thickness on OCT in all patients post anti-VEGF injection. However, only three out of seven patients showed significant improvement in visual acuity post-treatment. Thus FFA and OCT may neither be of help in predicting nor assessing treatment response. Nevertheless, it is important to identify the subset of patients in the non-proliferative PFT group that could potentially benefit from anti-VEGF therapy.

FFA due to its inherent drawback is unable to show details of all the vascular layers of retina.[6] OCT-A is being used in analysing the various structural changes in the perifoveal vessels in PFT. Thorell *et al*.[8] showed presence of vascular network in the outer retina without associated exudation or haemorrhage. Various other vascular abnormalities demonstrated on OCT-A include tortuous deeper vessels that can be drawn together,[13] dragging of vessels temporally toward an epicentre,[6] deep capillary network showing widely spaced dendritic appearance and increased open spaces in the superficial capillary plexus.[5] All these structural abnormalities in the vascular network which could not be picked up on FFA and thus possibly making OCT-A an important tool in enhancing our understanding in the pathogenesis of PFT.

Some of the features of type A net described here were also documented by Gass and Blodi in non-proliferative PFT on FFA. Gass and Blodi has documented presence of capillary ingrowth into FAZ, diffuse staining at the level of mid to outer retina and presence of peculiar branching vessels.[14] All these features were seen in some patients with non-proliferative PFT comprising type A net on OCT-A and can be important to predict treatment response as discussed subsequently.

We noted that patients with type A net tend to show significant visual acuity improvement with anti-VEGF treatment. The treatment response was also validated on subsequent OCT-A scans in the form of decrease in the size of net. The decrease in size of nets was validated by measurement of each of the nets by two independent observers and calculating ICC. An ICC score of >0.75 is considered as excellent correlation between the observers.[15] On the contrary,

type B vascular net did not show any change in visual acuity or vascular network size/density with anti-VEGF therapy. Hence, treating patients based on the type of net seen on OCT-A will help in better predicting possible treatment outcomes while preventing over treating of patients unlikely to benefit from anti-VEGF therapy.

Both type A and B nets correspond to the area of hyperpigmentation when present. They were seen more commonly temporal to fovea. The possible reason for this can be explained by the chronic nutritional damage leading to death of Müller cells and associated photoreceptors in that area. The damage to Müller cells disrupts the VEGF control leading to formation of abnormal vascular nets. Loss of photoreceptor cells permits retinal pigment epithelium (RPE) cells to migrate into overlying retina. However, no temporal relation was seen between the two. Both abnormal nets (type A and B) and hyperpigmentation were also noted to be present independent of each other.

Gass and Blodi[2] theorised that vision loss in patients with PFT from stage 1 to 4 is because of degeneration of retinal cells induced by nutritional deprivation rather than exudation. The author's hypothesise that the drop in vision in patients with PFT is due to two main factors: photoreceptor degeneration and neovascularisation existing concurrently. The disease course of PFT wherein SRNVM develops only after stage 4 may not always be true. Neovascularisation is a complication that can occur at any stage (1–4) in the course of PFT.

The limitations of the study include a small sample size and retrospective nature of the study. The presence of SRNVM was evaluated based on clinical examination and SD-OCT. FFA was not done at the time of initial assessment or on follow up.

Conclusion

OCT-A can play an important role in making early treatment decisions and help identify subset of patients with non-proliferative PFT that are likely to respond to anti-VEGF therapy. Even in the absence of clinical evidence of SRNVM, treatment based on presence of type A nets results into significant improvement of vision. In this study, we have shown presence of two abnormal vascular nets in patients with PFT type 2A and also points for differentiating the two. However, further evaluation of the changes in these vascular nets during anti-VEGF therapy and their relationship to other structural changes is warranted.

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Conflicts of interest

There are no conflicts of interest.

References

1. Yannuzzi LA, Bardal AM, Freund KB, Chen KJ, Eandi CM, Blodi B, *et al.* Idiopathic macular telangiectasia. Arch Ophthalmol 2006;124:450-60.
2. Gass JD, Blodi BA. Idiopathic juxtafoveolar retinal telangiectasis. Update of classification and follow-up study. Ophthalmology 1993;100:1536-46.
3. Engelbrecht NE, Aaberg TM Jr., Sung J, Lewis ML. Neovascular membranes associated with idiopathic juxtafoveolar telangiectasis. Arch Ophthalmol 2002;120:320-4.
4. Charbel Issa P, Holz FG, Scholl HP. Findings in fluorescein angiography and optical coherence tomography after intravitreal bevacizumab in type 2 idiopathic macular telangiectasia. Ophthalmology 2007;114:1736-42.
5. Roller AB, Folk JC, Patel NM, Boldt HC, Russell SR, Abramoff MD, *et al.* Intravitreal bevacizumab for treatment of proliferative and nonproliferative type 2 idiopathic macular telangiectasia. Retina 2011;31:1848-55.
6. Spaide RF, Klancnik JM Jr., Cooney MJ. Retinal vascular layers in macular telangiectasia type 2 imaged by optical coherence tomographic angiography. JAMA Ophthalmol 2015;133:66-73.
7. Spaide RF, Klancnik JM Jr., Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol 2015;133:45-50.
8. Thorell MR, Zhang Q, Huang Y, An L, Durbin MK, Laron M, *et al.* Swept-source OCT angiography of macular telangiectasia type 2. Ophthalmic Surg Lasers Imaging Retina 2014;45:369-80.
9. Charbel Issa P, Finger RP, Holz FG, Scholl HP. Eighteen-month follow-up of intravitreal bevacizumab in type 2 idiopathic macular telangiectasia. Br J Ophthalmol 2008;92:941-5.
10. Gamulescu MA, Walter A, Sachs H, Helbig H. Bevacizumab in the treatment of idiopathic macular telangiectasia. Graefes Arch Clin Exp Ophthalmol 2008;246:1189-93.
11. Nishijima K, Ng YS, Zhong L, Bradley J, Schubert W, Jo N, *et al.* Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. Am J Pathol 2007;171:53-67.
12. Yourey PA, Gohari S, Su JL, Alderson RF. Vascular endothelial cell growth factors promote the *in vitro* development of rat photoreceptor cells. J Neurosci 2000;20:6781-8.
13. Spaide RF, Klancnik JM Jr., Cooney MJ, Yannuzzi LA, Balaratnasingam C, Dansingani KK, *et al.* Volume-rendering optical coherence tomography angiography of macular telangiectasia type 2. Ophthalmology 2015;122:2261-9.
14. Agarwal A. Macular dysfunction caused by retinal vascular diseases. In: Agrwal A, editor. Gass' Atlas of Macular Diseases. 5th ed. Edinburgh: Saunders, Elsevier; 2012. p. 526-34.
15. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 1994;4:284-90.