MINERVA OFTALMOLOGICA

VOLUME 60 · No. 3 · SEPTEMBER 2018

EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA TRIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A. P. D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 0026-4903 TAXE PERÇUE

Online version at http://www.minervamedica.it

Minerva Oftalmologica 2018 September;60(3):85-97
DOI: 10.23736/S0026-4903.18.01801-9

REVIEW

OCT ANGIOGRAPHY: A NEW ERA OF OPHTHALMOLOGY

Optical coherence tomography angiography in clinical practice

Manish NAGPAL *, Rakesh JUNEJA

Department of Vitreo-Retina, Retina Foundation, Shahibagh, India

*Corresponding author: Manish Nagpal, Department of Vitreo-Retina, Retina Foundation, PO Box 380004, Near Shahibag Underbridge, Shahibag, Ahmedabad, Gujarat, India. E-mail: drmanishnagpal@yahoo.com

ABSTRACT

Optical coherence tomography angiography (OCTA) is a novel non-invasive tool that works on the principle of "decorrelation." It is built on the platform of optical coherence tomography (OCT). It is still in its infancy and has a tremendous potential applicability for diagnosing retinal and choroidal vascular diseases. Its non-invasive nature and the ability to generate images of retinal and choroidal vasculature allows it to replace and/or supplement the current angiographic gold standards, fluorescein angiography (FA) and indocyanine green angiography (ICGA), if not in all but certainly in most of retinal and choroidal pathologies. Still there exists a major challenge in terms of its wide scale availability, equipment and processing techniques, presence of artifacts, limitations of imaging capability, lack of common vocabulary among retinal specialists for interpretation. In this review we intend to describe this novel technique by highlighting its principle, comparison with FA and ICGA, its applicability in various clinical scenarios like diabetic retinopathy, age related macular degeneration, retinal venous occlusion, choroiditis, in routine practice. However, further studies are needed to more definitively determine OCTA's utility in the clinical setting and to establish if this technology may offer a non-invasive option of visualizing the retinal vasculature in detail.

(*Cite this article as:* Nagpal M, Juneja R. Optical coherence tomography angiography in clinical practice. Minerva Oftalmol 2018;60:85-97. DOI: 10.23736/S0026-4903.18.01801-9)

KEY WORDS: Optical coherence tomography - Fluorescein - Indocyanine green - Diabetic retinopathy - Macular degeneration - Choroiditis.

Optical coherence tomography (OCT) is a revolutionary imaging modality that allows morphologic and quantitative assessments of retinal structure. Fluorescein angiography (FA) is an invasive, time-tested, gold standard procedure for studying retinal vasculature and helps to delineate various retinal pathologies. However, both OCT and FA have certain limitations that significantly affect our ability to understand pathology and, consequently, to determine prognosis and management.[1] Building on the platform of OCT and based on the principle of "decorrelation," OCT angiography (OCTA) is a novel, non-invasive tool that uses interferometric analysis of short-coherence-length light reflected from moving blood within the retina and choroid and calculates the variation over time of reflectance parameters (*e.g.*, amplitude or phase).[2, 3] It can also generate 3D maps of microvasculature flow pattern from retinal capillary plexus and choroidal vasculature, and these capabilities have enabled us to better understand, analyze, and treat a number of retinal pathologies.[1, 3]

Principle of OCTA

OCTA involves principle of "decorrelation." It uses interferometric analysis of short-coherence-

length light reflected from moving blood within the retina and choroid and calculates the variation over time of reflectance parameters (*e.g*., amplitude or phase).[1] Volumetric information is generated by sequentially acquiring multiple B-scans which are displaced perpendicular to the B-scan image, covering a region of the retina or anterior eye using raster scan. The retina is a stationary object for the most part, so if successive B-scans at the same position are acquired, they will be largely similar, except for the motion of blood within the tissue. At the sites of blood flow, the reflectivity or scattering changes from one scan to the next. By comparing repeated OCT B-scans, it is possible to image blood flow by looking for differences among the scans on a pixel-by-pixel basis.[1] OCTA can generate 3-D maps of microvasculature flow pattern from retinal capillary plexus and choroidal vasculature, and its capabilities have enabled us to better understand, analyze, and treat a number of retinal pathologies.[4, 5]

History of OCTA development

The arrival of OCTA in ophthalmic world occurred around a decade ago. Previously studies used to detect and measure blood flow by Doppler techniques, which compared the phase of successive OCT A-scans.[6, 7] Zhao *et al*. in their study published around 15 years ago told that the blood vessels could be visualized using Doppler OCT with time domain OCT by extracting and comparing the A-scan phase changes which are related to the Doppler frequency shift. This method was known as optical doppler tomography and was demonstrated for dermatological imaging of blood vessels in the skin.[8] Later on, as the time passed by, further advancements in ophthalmic biomedical engineering and with the development of spectral domain OCT (SD-OCT), the phase of the A-scans became directly accessible and imaging speeds increased. It was in the year 2005, by Ahang and Chen who demonstrated that blood flow could be visualized using swept source OCT (SS-OCT) by measuring the variance of the Doppler signal and intensity variation without phase.[9] These advancements led to, currently all over the world commercially available revolutionary tool, the OCTA.

Image acquisition in OCTA

A voxel by voxel calculation of decorrelated signals is done by OCTA imaging software. The software scans 256 voxels in the particular area of field selected by examiner, with eight B-scans repeated at each voxel.[10] Further, at each voxel the software performs 256 A-scans per B-scan, with a distance between B-scans of 10 μm. The number of B-scans performed per voxel and the number of A-scans per B-scan varies according to the software and the algorithm used. Algorithms incorporated into the software perform computations based on clusters of B-scans and generate flow patterns based on motion of erythrocytes within the vasculature. This results in the formation of *en-face* images retinal capillary network and choroidal vasculature at various levels.[5, 6]

Relishing the challenge of imaging the living eye by OCTA

Optical coherence tomography angiography visualizes blood flow by detecting erythrocyte motion; however, the eye itself moves, so one of the major challenges is to detect erythrocyte motion separately from parasitic eye motion. The blood flow in capillaries is on the order of 1.5 to approximately 3 mm/s,[11, 12] and the erythrocytes travel in single file. To produce an image that is 300×300 pixels, each fundus position has to be scanned at least twice to detect any type of change. The OCT beam has to be scanned across this region in a raster fashion, which itself incurs overhead in terms of wasted time during the beam scanning process. The newest commercial spectral domain OCT instruments operate at 70,000 A-scans per second and can acquire the 90,000 required A-scans twice in approximately 3 seconds. At 70,000 A-scans per second, it takes approximately 0.005 seconds to acquire each B-scan (300 A-scans), and each B-scan is performed twice, so the time between scans is $0.005 seconds. Therefore, to detect a $ 2 mm/second blood flow, the system needs to be able to detect 0.01 mm (10 mm) of movement in 0.005 seconds. Disease states may cause a slower blood flow,[13] so the lower limit of detection needs to be much smaller than 0.01 mm. Creating a method

that can detect 0.01 mm of movement in the allotted time is a challenge and is even more complicated because the eye-being imaged is connected to a living organism. Optical coherence tomography instruments use mirrors, so imaging the undead is not possible. A big problem is that methods which are highly sensitive to motion of blood can also be highly sensitive to eye motion of patient, which is called bulk motion. Methods using phase information for motion contrast are especially sensitive to bulk motion, and some research groups use bite plates to help stabilize the subject's head. Amplitude decorrelation methods may be less sensitive to bulk motion effects.

Various technologies in OCTA (spectral domain *vs.* swept source OCTA)

Spectral domain OCT (SD-OCT) for the purpose to capture the images uses a spectrometer and a line scan camera. The limited spectrometer resolution causes the detection sensitivity to vary for OCT signals at different axial ranges, a phenomenon known as sensitivity roll off.[3] The various commercial OCT instruments typically operate at 70,000 axial scans per second. Swept source OCT (SS-OCT) uses a frequency swept laser and a high-speed detector, without requiring a spectrometer. The sensitivity roll-off is much less in SS-OCT compared with SD-OCT because frequency swept lasers can have narrow frequency line-widths. Although the detection system for SS-OCT is less expensive than the spectrometer and line scan camera used for SD-OCT, laser light sources used in SS-OCT are currently expensive, making SS- OCT costlier.

Historically, OCT imaging was performed at 840 nm because super-luminescent diode light sources used for laser gyroscopes were at these wavelengths. Longer wavelength light at 1050 nm has been shown to have reduced the attenuation from ocular opacities and improved penetration into the choroid.[14] It was demonstrated that 1050 nm wavelengths can have superior image penetration and less attenuation than 840 nm wavelength.[3] But since the SS-OCTA is yet to be widely available commercially, the SD-OCTA continues to be the most commonly available and widely used tool.

Understanding the OCTA Projection artifacts

One of the major challenge to date is the presence of projection artifacts in OCTA images. It is very important to understand the genesis of these artifacts. Genesis of OCTA images involves light passing through a blood vessel that can be either reflected, refracted, or absorbed. The light reflected from moving blood cells forms the basis of OCTA. However, the light that has passed through moving blood also encounters tissue below the blood vessel. When this light strikes the retinal pigment epithelium (RPE), it is reflected back to the OCT instrument. The light that has passed through the blood vessels changes over time, and so the reflection of this light is detected as having a decorrelation resembling blood flow. Therefore, the RPE will seem to have blood vessels that have the pattern of the overlying retinal blood vessels. We refer to this effect as an OCTA projection artifact.

Optical coherence tomography projection artifacts also occur from superficial retinal vessels, which can be seen in deeper retinal layers, or retinal and choroidal vessels, which can be even seen deep in the sclera. The OCTA projection artifacts are nearly always present and seen in any structure that is located below vasculature.

Understanding OCTA projection artifacts is important for accurate clinical assessment. For example, using OCTA to detect choroidal neovascularization may offer the possibility of patient diagnosis and follow-up without the need for FA. As such, we could image suspicious elevations, and even in the absence of new vessels, we might see fragments of images of the overlying retinal vessels. As another example, intraretinal pigment migration may serve as a reflecting point to suggest the presence of intraretinal neovascularization. Optical coherence tomography angiography projection artifacts can be readily identified by examining sequential en face images at different depths. Projection artifacts will cause superficial vessels to be seen in en face images, which are below the vessel, although the vessel has a limited axial depth. Some OCTA software implementations remove OCTA projection artifacts by subtracting them from images below. Snodderly estimated that 45% of photons passing through the perfoveal macula go through

a blood vessel; and around the nerve, the proportion is approximately 70%.[15, 16] If a simple software algorithm was used to suppress projection images derived from the inner retina, then a significant proportion of the pixels external to the retinal vessels would be suppressed or altered in some way by the algorithm. This creates the opportunity for a whole new set of image artifacts.

Although OCTA projection artifacts can be a hindrance, they also can be exploited. In fibrovascular pigment epithelial detachments, particularly those that have been treated with antivascular endothelial growth factor, there are several layers.[17-19] The inner most is the RPE, under this are the neovascular vessels, and deeper there appears to be a layer of fibrotic tissue. If the *en-face* OCTA image is taken through the vessels themselves, the RPE will be included, and then by default, the projection images from the retinal vessels will also be seen. If the *en-face* section is taken deeper, at the outer border of the vessels to include the fibrotic tissue, an image that is mostly composed of the projection from the neovascular vessels will be formed. In this case, the best way to see the vessels is not to look directly at them, but to look at their projection.

The potential OCTA artifacts and what we are really seeing is a source of confusion when it comes to imaging the choriocapillaris. The choriocapillaris is located below and is separated from RPE by Bruch's membrane. The basement membrane of the RPE and that of the choriocapillaris form the outer layers of Bruch's membrane, which typically is 2 to 4 mm thick. Ramrattan *et al*.[20] measured the chorioca- pillaris thickness in autopsy eyes and found it ranged from 9.8 mm in the first decade of life to 6.5 mm in the tenth decade. When the image plane is selected to be at the level of the RPE, the projection image from the retinal vessels is seen. If an imaging slab is selected at the level where the choriocapillaris is expected to be, the retinal vessels dominate the image. If the section is moved deeper, to the hyporeflective region in the structural OCT where small vessels connecting up to the choriocapillaris are expected to be seen, OCTA shows a fine interconnected layer of vessels suggestive of the choriocapillaris without the retinal vascular projection image. Some of the vessels in this image look too large to be in the choriocapillaris, but the sheet of apparent high flow implies that there is an OCTA projection from the choriocapillaris onto the deeper structures. Conversely, overlying pathologic study, such as large drusen or pigment epithelial detachments can attenuate the OCT signal making regions of the choriocapillaris seem absent, although flow is likely to be present.[21]

Comparison of OCTA and FA

Fluorescein angiography (FA) and indocyanine green angiography (ICGA) are both invasive test that require intravenous administration of dye and imaging up to 10-30 minutes.[22-26] They provide two-dimensional image sets that allow for dynamic visualization of blood flow with a wide field of view. Therefore, patterns of dye leakage, pooling, and staining can be appreciated and are well-documented in the literature.[27]

FA remains the gold standard for the detection of choroidal neovascularization (CNV), as well as retinal neovascularization such as neovascularization of the disc (NVD) and neovascularization elsewhere (NVE).[28-31] However, retinal pathology can be obscured by this leakage as well as hemorrhage or media opacities, and localization of the depth of the lesion and size delineation of neovascularization can be difficult due to dye leakage and poor stereopsis, and because the imaging modalities are not depth resolved. As a result, segmentation of different layers is not routinely possible with FA or ICGA.[31]

FA and ICGA have other drawbacks that can limit their widespread use. Since they are invasive, relatively expensive, and time-consuming, they are not ideal techniques to use on a regular basis in a busy clinical setting. Although considered safe, the dyes pose risks ranging from nausea to allergic reactions, including anaphylaxis in rare instances. Aside from allergic reactions of which the likelihood increases with frequency of use, indocyanine green dye is contraindicated in pregnancy and kidney disease. For the evaluation of patients requiring frequent follow-up exams or of those that may not tolerate injection of intravenous dye, a rapid non-invasive technique to visualize retinal and choroidal vessels would be beneficial.[32-34]

OCTA in comparison is a non-invasive tech-

TABLE I.—*Comparison of FA, ICGA, and OCTA.*

Feature		FA and ICG	OCTA
1.	Invasive	Yes	No
2.	Duration	More (around 20-30 minutes)	Less (around 10-15 minutes)
3.	Visualization	2. D	3. D
4.	Pattern	Dynamic	Static
5.	Vascular network studied	Superficial (ILM to outer border to IPL)	Superficial (ILM to outer border of IPL) Deep (inner border of IPL to OPL) Avascular area (OPL to RPE) Choriocapillaris
6.	Gold standard	YES	NO
7.	Repeatability	Less	More
8.	Complications	Yes	No
9.	Contraindications	Renal parameters Pregnancy	No
10.	Expensive	More	Less
11.	Field of view	Large	Small
12.	Resolution	Less	More (3×3 mm cube)
13.	Stereopsis	Poor	Good
14.	Mydriasis	Mydriatic	Non-mydriatic

ILM: internal limiting membrane; IPL: inner plexiform layer; OUP: outer plexiform layer; RPE: retinal pigment epithelium.

nique that acquires volumetric angiographic information without the use of dye. Each three-dimensional scan set takes less few seconds to obtain. The *en-face* images (OCT angiograms) can then be scrolled outward from the internal limiting membrane (ILM) to the choroid to visualize the individual vascular plexus and segment the inner retina, outer retina, choriocapillaris, or other area of interest.

The *en-face* acquisition areas currently range from 2×2 mm to 12×12 mm with the scan quality greatly decreased with a widened field of view since the same number of OCT b-scans is used for all scanning areas. The 12×12 mm scan is only available on research prototypes. The 3×3 mm OCT angiograms appear to be higher resolution than the currently available FA/ICGA images, and a study by Matsunaga *et al.* deduced that they were at least equivalent in showing important vascular detail.[35, 36] The comparison between FA, ICGA, and OCTA have briefly mentioned in Table I.

OCTA in the clinical practice

OCTA in normal eyes

OCTA by computing consecutive B-scan images generates information by displaying vasculatures, which includes superficial capillary plexus in combination with intermediate and radial peripapillary capillary plexus, deep capillary plexus, avascular zone, choriocapillaris and choroid. The extent to which these vasculatures can be studied vary among different software provided by different companies and include cube sizes most commonly starting from 3×3 mm to 12×12 mm OCT angiograms (Figure 1, 2, 3).

OCTA in diabetics

FA and OCT help to understand various features of DR (NPDR and PDR) and play a very

Figure 1.—Color fundus photograph in normal eye of normal subject.

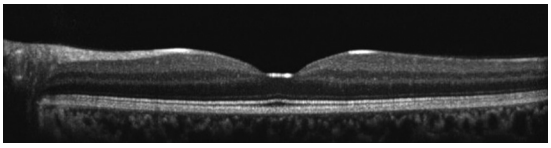

Figure 2.—OCT in the same subject showing normal foveal contour.

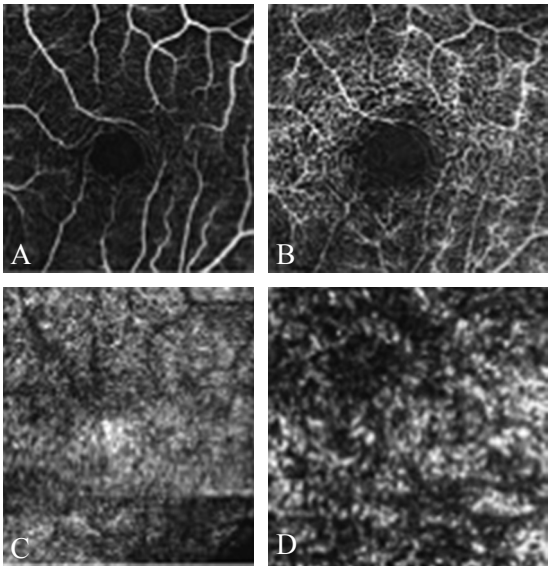

Figure 3.—OCT angiography in normal eye of a normal subject showing various retinal and choroidal vasculature's superficial capillary plexus (A), deep capillary plexus (B), avascular zone (C), choriocapillaris (D).

important role in its management. But due to its invasive nature FA cannot be done in each and every patient and OCT has its own limitations in providing the required information. OCTA is a promising non-invasive modality to identify features that helps to diagnose various stages ranging from mild non-proliferative DR (NPDR) to a fully established proliferative diabetic retinopathy (PDR).[37, 38] However, OCTA in the presence of presence of vitreous-haemorrhage fails to provide the desired information since the signals can't approach the underlying retinal surface and the scans cannot be obtained. The various features that can be elucidated by OCTA in DR include microaneurysms, retinal capillary perfusion density, hard exudates, FAZ measurement, capillary tortuosity and dilation, early NVE and NVD.[39, 40] It also has the ability to show the architecture of neovasculature underlying the leakage (Figure 4, 5).

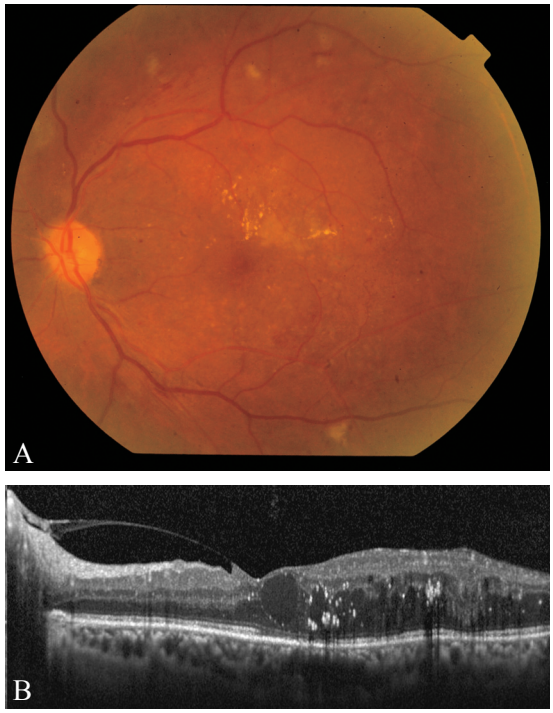

Figure 4.—A) Color fundus photograph of left eye in a case of non-proliferative diabetic retinopathy showing microaneurysms, dot-blot hemorrhages, hard exudates and CSME; B) OCT in the same subject showing altered foveal contour, taut posterior hyaloid causing traction at fovea, cystoid spaces, hard exudates.

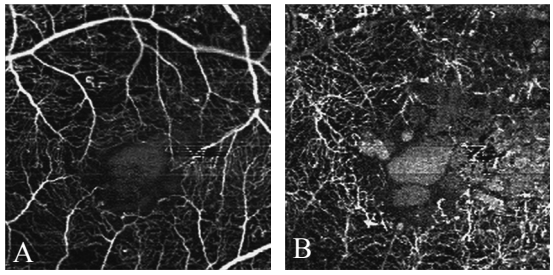

Figure 5.—OCT angiography in a case of non-proliferative diabetic retinopathy showing features as altered FAZ, increased decorrelation signals representing microaneurysms in superficial (A) and cystoid macular edema (B) along with features of superficial capillary plexus which are more prominent in deep capillary plexus.

OCTA in AMD

The predominant feature is choroidal neovascularization (CNV) in which can result in hemorrhage, fluid exudation, and fibrosis, resulting in photoreceptor damage and vision loss. FA is the most predominantly employed tool for the pur-

pose of diagnosis but in lieu of its invasive nature and various side effects, OCTA because of its non-invasive nature can be used an alternative non-invasive tool. It also helps to understand the CNV membrane's morphology and pattern.

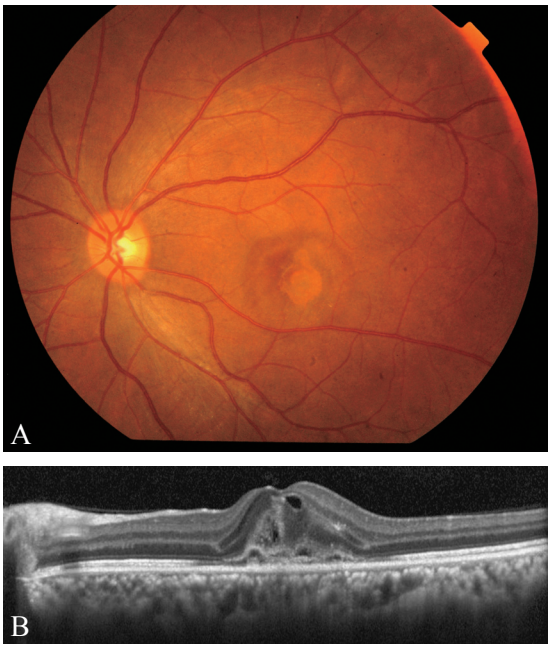

Figure 6.—A) Color fundus photograph of left eye in a case of age-related macular degeneration showing altered foveal reflex with subretinal neovascular membrane; B) OCT in same subject showing altered foveal contour with subfoveal hyper-reflectile membrane.

Figure 7.—OCT angiography in a case of choroidal neovascular membrane secondary to age-related macular degeneration case showing increased decorrelation signal representing prominent neovascular network at the level of choroid.

Coscas *et al*.[41] on OCTA findings, have classified wet AMD into the following patterns:

- a well-defined (lacy-wheel or sea-fan shaped) CNV lesion in contrast to one with long filamentous linear vessels;
- branching, numerous tiny capillaries, typical of a recent lesion, in contrast to rare large mature vessels, typical of a mature one;
- presence of anastomoses and loops;
- morphology of the vessel termini, assessing the presence of a peripheral arcade in contrast to a "dead tree" appearance;
- presence of a perilesional hypointense halo considered as regions of choriocapillaris alteration, either corresponding to flow impairment steal or localized atrophy (Figure 6, 7, 8A).

OCTA in IPCV

Indocyanine green angiography (ICGA) is considered as the gold standard test for diagnosing and management of IPCV.[42] Polypoidal lesions and branching vascular networks in IPCV characteristically appear as hyper-flow round structures on OCTA (Figure 8B, 9, 10, 11). However, in certain cases, hypo-flow structures are also observed. This absence of signal does not mean that there is no blood flow; rather, it indicates that blood flow is not within the detection limit of the OCTA device. This could be due to either increased or decreased flow in the polyps and subsequent non-visualization of the vascular structure. Further improvements in OCTA knowledge are needed to gather information on the specificity of the different intensity characteristics of polypoidal lesions.[36]

OCTA in MacTel

Macular telangiectasia type 2 (MacTel2) is a neurodegenerative disease which is characterized by loss of Muller cells of the macular area.[43] Various signs that occur in due course of progression include whitening of the inner retina, crystal deposits in the nerve fiber layer, breakdown of the external limiting membrane/ellipsoid zone, cyst formation in the inner retina, cavitation of the outer retina, perifoveal capillary leakage, parafoveal venular dilation, pig-

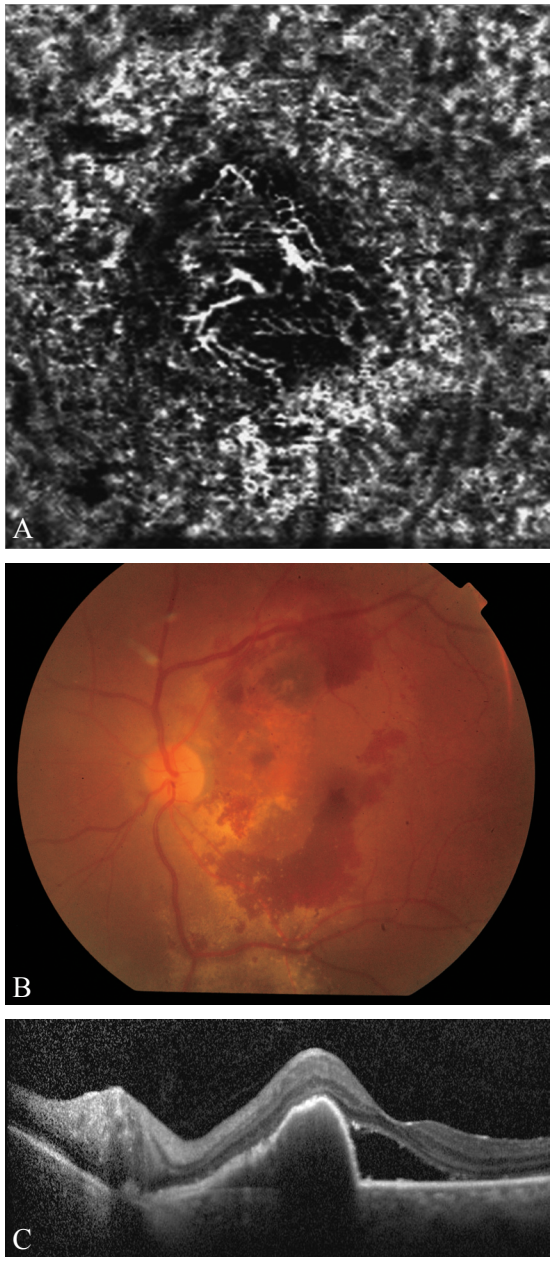

Figure 8.—A) Color fundus photograph of left eye in a case of polypoidal choroidal vasculopathy showing altered foveal reflex with subretinal hemorrhage and neovascular membrane; B) OCT in same subject showing altered foveal contour with PED and sub-retinal fluid; C) fluorescein angiography of same subject showing hyperfluorescence at posterior pole predominantly along the nasal border of FAZ which increases in size and intensity suggestive of leakage.

ment proliferation in the retina, and subretinal neovascularization.[44]

On OCTA, the retinal vascular pathology in the deep capillary network includes enlargement of vessels and larger intervascular spaces, dilated, dendritic appearance of vessels, telangiectasia, reduction and/or loss of capillary density, and the presence of anastomoses toward the superficial capillary network (Figure 12, 13, 14).[45]

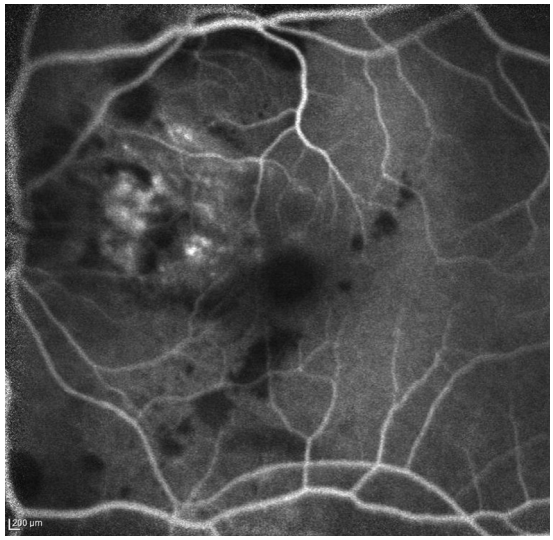

Figure 9.—Indocyanine green angiography showing an area of hypofluorescence at posterior pole with multiple hyperfluorescent polypoidal lesions arranged in a chain like fashion representing the presence of branch vascular network.

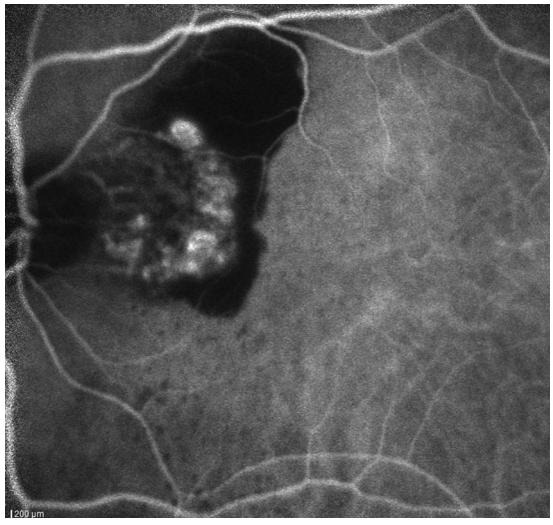

Figure 10.—OCT angiography showing decreased decorrelation signal corresponding to hypofluorescence at posterior pole and increased decorrelation signal arranged in a polyp-like fashion with similar morphological appearance as the hyperfluorescence lesions in ICGA and at the similar topographical locations representing it non-invasively.

Figure 11.—Color fundus photograph OS with MacTEL IIA Stage 5 (proliferative stage) showing right angled deflection of venules, temporal parafoveal retinal elevation with subretinal fluid, mild subretinal lipid exudation, and subretinal blood characteristic of the onset of subretinal neovascularization.

Figure 12.—Optical coherence tomography OS with MacTEL IIA Stage 5 showing retinal thickening temporal to fovea, disruption and loss of photoreceptors and IS/OS junction, sub-retinal fluid, an intraretinal highly reflective area temporal to the fovea corresponding to RPE proliferation, fusiform thickening and duplication of the highly reflective RPE/choriocapillaris complex corresponding to choroidal neovascularization.

OCTA in choroiditis

ICG is considered as test of choice for assessing active and healing choroiditis lesions but being an invasive procedure, it carries certain risks.

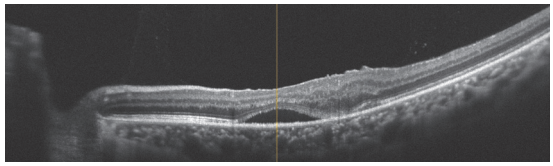

Figure 13.—Fundus fluorescein angiography OS with MacTEL IIA Stage 5 featuring subretinal neovascularization, temporal to the foveal center, that is rapidly hyperfluorescent in the early stage, increasing in fluorescence and leaking intensely in the late phase. The capillary telangiectasia is also easily visible at this stage of the disease, demonstrating early capillary wall staining and late intraretinal staining that differs in character form the more intense late hyperfluorescent leakage of the subretinal neovascularization.

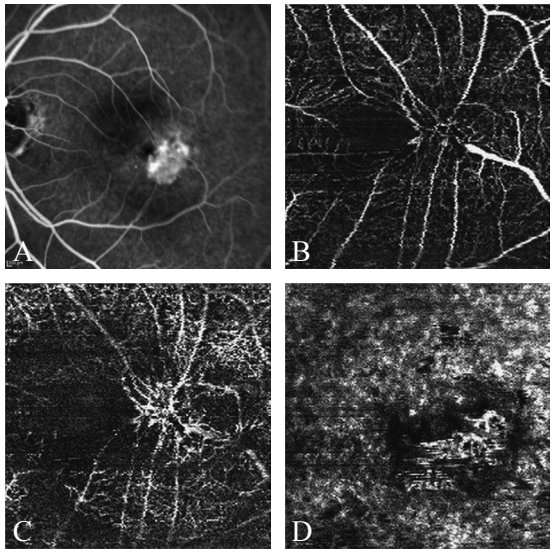

Figure 14.—Optical coherence tomography angiography OS with MacTEL IIa Stage 5 featuring superficial capillary plexus (A) and deep capillary plexus (B) (INL to OPL) that demonstrates retinal vascular anastomoses in the temporal juxtafoveal region (telangiectatic vessels) with distortion of the capillary plexus and microvascular abnormalities and choroid and choriocapillaris (C, D) (below RPE-Bruch's membrane) that demonstrates evidence of a plaque/network with abnormal microvascular flow in the outer retina that corresponds to subretinal neovascularization.

OCTA non-invasively can provide features corresponding to ICGA in both during the active and healing phases.

There are very few studies in literature that have shown the features of choroiditis lesions on OCTA and have compared the features of active and healing lesions with ICGA both pre and post treatment. Mandadi *et al*.[46] have described the comparative features of OCTA and ICGA in serpiginous like choroiditis (SLC) both

during and active and healing phases. In active phase, SLC lesion on OCTA, appear as areas of large flow void or decreased decorrelation signals corresponding to hypofluorescent area on ICGA at similar topographic locations. Simultaneously, in healing phase these lesions appear as reduced areas of large flow void or reduced "decreased decorrelation signals" corresponding to reduced hypofluorescent area on ICGA (Figure 15 A-C).

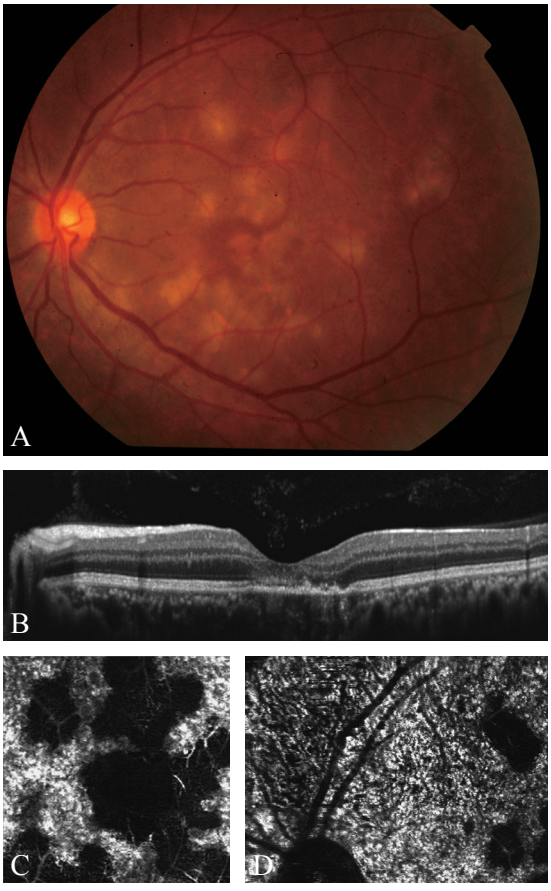

Figure 15.—A) Color fundus photograph of left eye in a case of serpiginous like choroiditis showing altered foveal reflex with multiple subretinal yellowish-white lesions extending up to arcades, irregular in shape, and with ill-defined margins; B) OCT in the same subject showing normal foveal contour, altered PR and RPE layer with thickened choroid; C) OCT angiography in a case of active serpiginous like choroiditis showing large flow void area in the form of decreased decorrelation signal involving the macula; D) OCTA panorama of the same subject, showing 12×9 mm area encompassing 30×40 degrees field of view from fovea in a case of active serpiginous like choroiditis involving macula showing multiple flow void area involving the macula.

Panoramic OCTA

OCTA software incorporated by various companies can scan only a certain field of view in various sizes of cube based on examiner preference and on the location and size of pathology. The fields of view used most frequently are 3×3 mm and 6×6 mm. However, in general one can expand a maximum to 9×9 mm and 10×10 mm. As the examiner selects the larger field of view, the resolution of images keeps on decreasing.[1]

The AngioScan OCT Angiography software on the RS-3000 Advance OCT (Nidek) allows clinicians to compose panoramic images with larger fields of view — 12×9 mm, 9×9 mm, 6×6 mm, and 4.5×4.5 mm — providing, respectively, 40°×30°, 30°×30°, 20°×20°, and 15°×15° fields of view (Figure 15D). In each of these sizes of fields of view, the software splits the scanning area into 3×3-mm cubes. The resolution obtained is therefore the same as that of an individual 3×3-mm cube provided by other software, but a larger field is simultaneously scanned at the same time. The large fields of view provided by panoramic imaging software now enabled us to non-invasively capture features previously seen only with FA. It also allows a real time comparison with ICGA and FA images and is particularly useful to capture lesions in choroiditis, PDR and various other diseases, allowing highest possible resolution at the same time.[1]

Limitations of OCTA

In order to better understand the correlation and comparison of OCTA with invasive FA and ICGA, a large multi-centric multi-ethnic study comparing these tools, may also be instructive A major challenge is to develop automated repeatable segmentation algorithms that reliably identify specific retinal vascular layers, even in the diseased and poorly fixating eyes. Further limitations include suboptimal correction for eye motion artifacts and projection artifact from superficial vessels during imaging of deeper layers.

Distinguishing pathologic vessels from the normal vasculature may be challenging in certain cases. Moreover, the SSADA technique has relatively poor axial resolution (~15 μm) due to signal averaging, limiting the identification of

small-caliber vessels. Using the current commercially available technology, OCTA is more prone to artifacts than FA. The larger superficial retinal vessels cause a "ghost image" producing shadow artifacts, when segmenting deeper layers, especially in the outer retina. This can make it more difficult to appreciate the presence of abnormal vasculature in deeper layers and have a bearing on perfusion index.

Because OCTA uses the principle that movement in the back of the eye represents blood flow, it is prone to motion artifact. White lines (representing decorrelation signals) appear in areas of the scan if the patient loses fixation or moves. Conversely, blinks appear as a black line across the scan because the OCT signal is blocked from reaching the retina and the software, thus, detects no movement. Blood cells should be the only moving object in the retina and some non-vascular structures such as fine tissue may also cause a decorrelation signal, especially if the patient is moving or poorly fixating. OCTA may also miss areas of slow blood flow such as in micro-aneurysms or fibrotic CNV. Since OCTA relies on changes between consecutive B-scans, it will detect flow only above a minimum threshold, the slowest detectable flow, which is determined by the time between the two sequential OCT B-scans. Consequently, lesions which have flow below the slowest detectable flow cannot be visualized using this imaging technique. Increasing the time between consecutive OCT B-scans could allow for increased flow detection while it would offer a trade-off due to increased movement artifact. Finally, it remains unknown how the additional information gained from this technique can be used in routine clinical practice.[47]

Conclusions

The need for a non-invasive imaging modality, along-with concurrent developments in the field of bio-medical engineering led to the emergence of a non-invasive tool named optical coherence tomography angiography. The basic underlying principle is "decorrelation" and it has several advantages over conventional invasive techniques Fluorescein angiography and Indocyanine green angiography. Although, despite of its unique features, its potential applicability is under observation and this technology is very nascent and is continuously evolving. It is certainly at the moment a potential supplementary tool to FA and ICGA and an alternative at times for some of the pathologies, but it needs to evolve more with time and many long-term longitudinal studies are required to confirm its validity. Also, there is a lack of worldwide common vocabulary to understand the features among the examiners and interpreters but we are for sure looking towards a very exciting potential tool, which has the capacity to replace invasive tools with time and further developments.

Future trends

OCT angiography is a nascent technology and is still in its infancy. There are several indications in which OCTA is better than or equivalent to accepted approaches. None of these older imaging modalities can be replaced by OCTA at present. That raises questions about the need for OCTA. Despite the potential benefits of OCT angiography, our expectations of technology must be tempered, given our limited experience. Finally, it remains unknown how the additional information gained from this technique can be used in routine clinical practice. But it seems like OCTA is a truly disruptive technology. It is exciting and will probably change the approach of our practice of retinal diseases.

References

1. Nagpal M, Juneja R. Panoramic Imaging With OCTA. Retina Today 2017;12:48–52.

2. Nagpal M, Singh SS. OCT angiography in retinal and choroidal diseases. Retina Today 2016;11:57–64.

3. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res 2018;64:1–55.

4. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous 2015;1:5.

5. Zhang Q, Wang RK, Chen CL, Legarreta AD, Durbin MK, An L, *et al.* Swept source optical coherence tomography angiography of neovascular macular telangiectasia type 2. Retina 2015;35:2285–99.

6. Roisman L, Zhang Q, Wang RK, Gregori G, Zhang A, Chen CL, *et al.* Optical coherence tomography angiography of asymptomatic neovascularization in intermediate age-related macular degeneration. Ophthalmology 2016;123:1309–19.

7. Lumbroso B, Huang D, Fujimoto JG, Rispoli M, Jia Y. Clinical guide to angio-OCT: non invasive, dyeless OCT angiography. London: Jaypee Brothers Medical Publishers; 2015.

8. Chen Z, Milner TE, Srinivas S, Wang X, Malekafzali A, van Gemert MJ, *et al.* Noninvasive imaging of in vivo blood flow velocity using optical Doppler tomography. Opt Lett 1997;22:1119–21.

9. Izatt JA, Kulkarni MD, Yazdanfar S, Barton JK, Welch AJ. In vivo bidirectional color Doppler flow imaging of picoliter blood volumes using optical coherence tomography. Opt Lett 1997;22:1439–41.

10. Moult EM, Waheed NK, Novais EA, Choi W, Lee B, Ploner SB, *et al.* Swept-source optical coherence tomography angiography reveals choriocapillaris alterations in eyes with nascent geographic atrophy and drusen-associated geographic atrophy. Retina 2016;36(Suppl 1):S2–11.

11. Wolf S, Arend O, Toonen H, Bertram B, Jung F, Reim M. Retinal capillary blood flow measurement with a scanning laser ophthalmoscope. Preliminary results. Ophthalmology 1991;98:996–1000.

12. Funatsu H, Sakata K, Harino S, Okuzawa Y, Noma H, Hori S. Tracing method in the assessment of retinal capillary blood flow velocity by fluorescein angiography with scanning laser ophthalmoscope. Jpn J Ophthalmol 2006;50:25–32.

13. Sonkin PL, Kelly LW, Sinclair SH, Hatchell DL. Pentoxifylline increases retinal capillary blood flow velocity in patients with diabetes. Arch Ophthalmol 1993;111:1647–52.

14. Povazay B, Hermann B, Unterhuber A, Hofer B, Sattmann H, Zeiler F, *et al.* Three-dimensional optical coherence tomography at 1050 nm versus 800 nm in retinal pathologies: enhanced performance and choroidal penetration in cataract patients. J Biomed Opt 2007;12:041211.

15. Weinhaus RS, Burke JM, Delori FC, Snodderly DM. Comparison of fluorescein angiography with microvascular anatomy of macaque retinas. Exp Eye Res 1995;61:1–16.

16. Snodderly DM, Weinhaus RS, Choi JC. Neural-vascular relationships in central retina of macaque monkeys (Macaca fascicularis). J Neurosci 1992;12:1169–93.

17. Rahimy E, Freund KB, Larsen M, Spaide RF, Costa RA, Hoang Q, *et al.* Multilayered pigment epithelial detachment in neovascular age-related macular degeneration. Retina 2014;34:1289–95.

18. Spaide RF. Enhanced depth imaging optical coherence tomography of retinal pigment epithelial detachment in age-related macular degeneration. Am J Ophthalmol 2009;147:644–52.

19. Spaide RF. Optical coherence tomography angiography signs of vascular abnormalization with antiangiogenic therapy for choroidal neovascularization. Am J Ophthalmol 2015;160:6–16.

20. Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PT. Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. Invest Ophthalmol Vis Sci 1994;35:2857–64.

21. Spaide RF, Fujimoto JG, Waheed NK. Image artifacts in optical coherence tomography angiography. Retina 2015;35:2163–80.

22. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. Circulation 1961;24:82–6.

23. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. Circulation 1961;24:82–6.

24. Kogure K, Choromokos E. Infrared absorption angiography. J Appl Physiol 1969;26:154–7.

25. Yannuzzi LA, Slakter JS, Sorenson JA, Guyer DR, Orlock DA. Digital indocyanine green videoangiography and choroidal neovascularization. Retina 1992;12:191–223.

26. Staurenghi G, Bottoni F, Giani A. Clinical Applications of Diagnostic Indocyanine Green Angiography. In: Ryan SJ, Sadda SR, Hinton DR, editors. Retina. London: Elsevier Saunders; 2013. p. 51–81.

27. Johnson RN, Fu AD, McDonald HR, Jumper M, Ai E, Cunningham ET, *et al.* Fluorescein Angiography: Basic Principles and Interpretation. In: Ryan SJ, Sadda SR, Hinton DR, editors. Retina. London: Elsevier Saunders; 2013. p. 2–50.

28. Do DV, Gower EW, Cassard SD, Boyer D, Bressler NM, Bressler SB, *et al.* Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study. Ophthalmology 2012;119:771–8.

29. Kotsolis AI, Killian FA, Ladas ID, Yannuzzi LA. Fluorescein angiography and optical coherence tomography concordance for choroidal neovascularisation in multifocal choroidtis. Br J Ophthalmol 2010;94:1506–8.

30. Do DV. Detection of new-onset choroidal neovascularization. Curr Opin Ophthalmol 2013;24:244–7.

31. Bressler NM, Bressler SB. Neovascular (Exudative or "Wet") Age-Related Macular Degeneration. In: Ryan SJ, Sadda SR, Hinton DR, editors. Retina. London: Elsevier Saunders; 2013. p. 1183–212.

32. Yuan A, Kaiser PK. Branch Vein Occlusion. In: Ryan SJ, editor. Retina. 5th ed. China: Saunders; 2013. p. 1029–38.

33. Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB, *et al.* Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. Ophthalmology 1991;98:1139–42.

34. López-Sáez MP, Ordoqui E, Tornero P, Baeza A, Sainza T, Zubeldia JM, *et al.* Fluorescein-induced allergic reaction. Ann Allergy Asthma Immunol 1998;81:428–30.

35. Matsunaga D, Yi J, Puliafito CA, Kashani AH. OCT angiography in healthy human subjects. Ophthalmic Surg Lasers Imaging Retina 2014;45:510–5.

36. Jia Y, Bailey ST, Wilson DJ, Tan O, Klein ML, Flaxel CJ, *et al.* Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. Ophthalmology 2014;121:1435–44.

37. Zhao Y, Chen Z, Saxer C, Xiang S, de Boer JF, Nelson JS. Phase-resolved optical coherence tomography and optical Doppler tomography for imaging blood flow in human skin with fast scanning speed and high velocity sensitivity. Opt Lett 2000;25:114–6.

38. Ishibazawa A, Nagaoka T, Takahashi A, Omae T, Tani T, Sogawa K, *et al.* Optical coherence tomography angiography in diabetic retinopathy: A prospective pilot study. Am J Ophthalmol 2015;160:35–44.e1.

39. Agemy SA, Scripsema NK, Shah CM, Chui T, Garcia PM, Lee JG, *et al.* Retinal vascular perfusion density mapping using optical coherence tomography angiography in normals and diabetic retinopathy patients. Retina 2015;35:2353–63.

40. Takase N, Nozaki M, Kato A, Ozeki H, Yoshida M, Ogura Y. Enlargement of foveal avascular zone in diabetic eyes evaluated by en face optical coherence tomography angiography. Retina 2015;35:2377–83.

41. Coscas GJ, Lupidi M, Coscas F, Cagini C, Souied EH. Optical coherence tomography angiography versus traditional multimodal imaging in assessing the activity of exudative age-related macular degeneration: A new diagnostic challenge. Retina 2015;35:2219–28.

42. Cheung CM, Yanagi Y, Mohla A, Lee SY, Mathur R, Chan CM, *et al*. Characterization And Differentiation Of Polypoidal Choroidal Vasculopathy Using Swept Source Optical Coherence Tomography Angiography. Retina 2017;37:1464–74.

43. Powner MB, Gillies MC, Zhu M, Vevis K, Hunyor AP, Fruttiger M. Loss of Müller's cells and photoreceptors in macular telangiectasia type 2. Ophthalmology 2013;120:2344–52.

44. Charbel Issa P, Gillies MC, Chew EY, Bird AC, Heeren TF, Peto T, *et al.* Macular telangiectasia type 2. Prog Retin Eye Res 2013;34:49–77.

45. Zeimer M, Gutfleisch M, Heimes B, Spital G, Lommatzsch A, Pauleikhoff D. Association between changes in macular vasculature in optical coherence tomography– and fluorescein– Angiography and distribution of macular pigment in type 2 idiopathic macular telangiectasia. Retina 2015;35:2307–16.

46. Mandadi SK, Agarwal A, Aggarwal K, Moharana B, Singh R, Sharma A, *et al.*; for OCTA Study Group. Novel Findings On Optical Coherence Tomography Angiography In Patients With Tubercular Serpiginous-Like Choroiditis. Retina 2017;37:1647–59.

47. Chalam KV, Sambhav K. Optical Coherence Tomography Angiography in Retinal Diseases. J Ophthalmic Vis Res 2016;11:84–92.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: July 2, 2018. - Manuscript received: June 7, 2018.