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Role of Optical Coherence Tomography Angiography in Following-up Choroidal Neovascular Membranes during the Course of Aflibercept Therapy

Ahmad R. Ziada[1*], Mostafa Abd El Latif Abo El Einen[1], Hamdy Abd El Azim El Koumy[1] and El Said Ibraheem El Dessouky[1]

[1]Department of Ophthalmology, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Authors ARZ and MAELAEE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors HAEAEK and ESIED managed the analyses of the study. Author HAEAEK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the mean area of choroidal neovascularization (CNV) and the flow area within the CNV and determine their value in monitoring the effect of aflibercept therapy.
Study Design: prospective, interventional study.
Place and Duration of Study: Tanta University Hospital in the period between March 2017 and March 2019.
Methodology: OCT angiography images were obtained using the AngioVue (Optovue Inc., CA, USA). For quantitative analysis of the mean area of CNV and the flow area within the CNV, the CNV was manually delineated with the help of the manufacturer's automated software, and the parameters of interest were automatically calculated and generated.
Results: The study included forty eyes of 40 patients, 14 females and 26 males, the mean age of patients was 69 ± 5 years. The mean baseline best-corrected visual acuity (BCVA) was 51.29 ± 14.80 ETDRS letters, which significantly increased to 63.41 ± 5.03 at week 36; p-value < 0.05. The

**Corresponding author: E-mail: dr_roshdy87@yahoo.com;*

mean area of choroidal neovascularization decreased significantly from baseline (2.72 ± 4.29 mm2) to week 36 (1.53 ± 1.07 mm2); p-value < 0.05. The the flow area within the measured CNV decreased significantly from baseline (2.28 ± 2.08 mm2) to week 36 (0.91 ± 0.63 mm2); p-value < 0.05.

Conclusion: The mean area of CNV and the flow area within the measured CNV are valuable biomarkers for following up CNV during treatment with aflibercept.

Keywords: CNV area; flow inside CNV; choroidal neovascular membrane; optical coherence tomography angiography.

1. INTRODUCTION

Optical coherence tomography angiography (OCTA) is a new, non-invasive device that can detect motion contrast by one of the following three methods (1) phase-based, (2) amplitude-based, and (3) complex amplitude-based, the third technique uses a combination of the first two techniques. Red blood cells should move for a sufficient distance in order to be detected by the OCTA scans, this leads to a limitation in the OCTA devices, which may not be able to differentiate between no flow and slow flow [1,2].

Two commercial platforms are present, the first one is the spectral-domain OCT (SD-OCT), with a wavelength about 840 nm, and the second one is the swept-source OCT (SS-OCT), with a longer wavelength of approximately 1050 nm.

OCTA image is en-face image that is produced by segmentation of the OCTA cube at a certain depth, then the data within the slab are converted to this en-face image [3,4].

Fluorescein angiography (FA) and Indocyanine green angiography (ICGA) were the standard devices for studying and analyzing retinal and choroidal vasculature. However, they are invasive and need an injection of intravenous dye, and allergic reactions can happen from the dye. However, OCTA is noninvasive and easy to use so, it can be done by any technician in each patient visit [5].

Also, OCTA can visualize the deep vasculature, which cannot be visualized by dye-based devices, especially the choriocapillaris layer, which cannot be seen by fluorescein angiography due to escape of the dye through the choriocapillaris [2].

However, dye-based devices have advantages, including dynamic evaluation of the vasculature and the capability of detection of dye leakage in cases associated with blood-retinal barrier disruption [5,6].

Coscas et al. [7] assessed the activity of CNV by OCTA. CNV was classified into either sea-fan appearance of active CNV and long filamentous vessels of inactive CNV. Also, multiple branching vessels indicate active CNV, but larger caliber vessels indicate inactive CNV. Also, peripheral anastomoses and peripheral vascular loops indicate an active membrane. However, all parameters assessed by Coscas et al were not quantitative parameters, so we tried to develop a quantitative parameter of CNV activity.

OCTA opens up the possibility of a mathematical description of CNV vascular pattern. This method may represent a valuable biomarker of CNV activity during the course of anti-VEGF therapy in addition to the already established parameters of activity such as visual acuity and subretinal and intraretinal fluid in OCT.

In this study, we aimed at evaluating the mean area of choroidal neovascularization (CNV) and the flow area within the measured CNV and determine their value in monitoring the effect of aflibercept therapy.

2. MATERIALS AND METHODS

This prospective interventional study included 40 AMD patients with treatment-naïve CNV at Tanta University Hospitals in the period from March 2017 to March 2019.

2.1 Inclusion Criteria

The study eye is treatment-naive.
Sufficiently clear media imaging.
Intraocular pressure (IOP) of 25 mmHg or less.
Prior focal corticosteroid treatment is allowed.

2.2 Exclusion Criteria

Any prior treatment of neovascular AMD.
Pregnant or breast- feeding women.
Presence of any end-stage disease, such as end-stage cancer which may prevent a subject from completing the study.

These subjects underwent imaging of both eyes with OCT angiography at baseline upon entering this study and complete ophthalmological evaluation including measurement of unaided visual acuity, best-corrected visual acuity (BCVA), slit-lamp biomicroscopy examination of the anterior segment, intraocular pressure measurement using Goldmann applanation tonometer and dilated fundus examination with an indirect ophthalmoscope.

The initial diagnosis of CNV and clinical activity was based on the clinical assessment and multimodal imaging protocol, including SD-OCT and OCTA evaluation. Fluorescein angiography and indocyanine green angiography were not routinely performed.

On SD-OCT, the following were considered signs of activity; the presence of subretinal hyper-reflective material or pigment epithelial detachment associated with intraretinal, subretinal, and/or sub-RPE fluid.

On OCTA, CNV presence was detected by the presence of neovascular network and the detection of a vascular decorrelation signal above the RPE, which represent type 2 CNV or the presence of the vascular decorrelation signal below RPE and in between the Bruch's membrane and RPE layers which represent type 1 CNV.

2.3 Intravitreal Aflibercept Treatment

Subjects were scheduled for intravitreal aflibercept injections (IAI) 2 mg/ 0.05 ml at baseline, week 4, week 8, week 12, week 16, and week 20. Additional injections were administered on an as-needed basis per Primary Investigator (PI) discretion during the remaining visits based on the presence of any intraretinal or subretinal fluid on OCT, retinal hemorrhage visualized on examination, reduction of BCVA by 5 or more ETDRS letters, or evidence of either increased area or vascular density of the neovascular membrane on OCT-angiography.

2.4 Intravitreal Injection Technique

All intravitreal injections were performed by a single surgeon (A.R.Z).

All patients were injected in the operating theater under aseptic conditions.

Local anesthetic drops were used, and 10% periocular povidone-iodine was applied to the eyelid, then 5% povidone-iodine was applied to the eye. A sterile speculum was inserted.

Intravitreal injection of 2 mg/ 0.05 ml of Aflibercept was given 4 mm from the limbus in phakic patients and 3.5 mm from the limbus in pseudophakic patients. The needle is passed to the direction of the center of the eye, and the anti-VEGF is injected.

Paracentesis was not required. No antibiotic was given before or after surgery.

2.5 Image Acquisition

OCT angiography images were obtained using the AngioVue (Optovue Inc., CA, USA), images were centered on the fovea after pupillary dilation, each cube consisting of 304 clusters of two repeated B-scans each contains 304 A-scans [8,9,10].

Only the scans with a signal strength index (SSI) more than 65 were included in the study.

To detect the neovascular membrane, the segmentation lines were adjusted to the inner and outer border of the lesion. Then manual correction of errors of segmentation was carried out for B-scans [10].

2.6 Optical Coherence Tomography Angiography Evaluation of Choroidal Neo-vascular Membrane

OCT angiography was performed at baseline, week 2, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, and week 36.

Quantitative analysis of the area of the CNV and flow inside the CNV lesion were performed using the automated manufacturer-provided software embedded in the AngioVue (Fig. 1).

3. RESULTS

Statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY). Wilcoxon signed-rank test was performed to test the difference between the studied parameter at baseline and at the end of follow-up. A p value $\leq$ 0.05 was considered to be statistically significant.

The study included forty eyes of 40 patients, 14 females and 26 males, the mean age of subjects was 69 ± 5 years.

The mean baseline best-corrected visual acuity (BCVA) was 51.29 ± 14.80 ETDRS letters, which significantly increased to 63.41 ± 5.03 at week 36; p-value < 0.05 (Table 1).

The mean area of the neovascular membrane (mm2) decreased significantly from baseline (3.08 ± 4.29) to week 36 (0.8 ± 1.07); p value < 0.05 (Table 1).

The mean flow area within the measured CNV (mm2) showed a similar statistically significant decrease from 2.28 ± 2.08 at baseline to 0.47 ± 0.63 at week 36; p-value < 0.05 (Table 2).

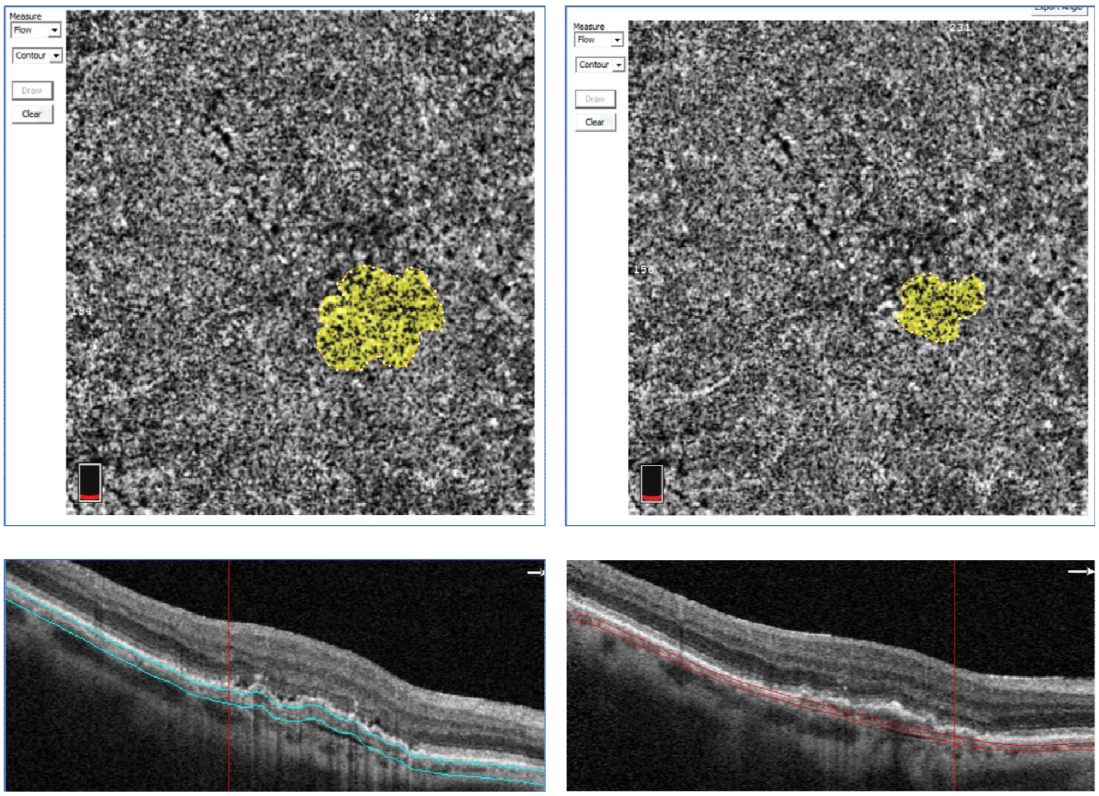

Fig. 1. The en-face Optical Coherence Tomography Angiography image (C-scan) showing the choroidal neovascular membrane was generated after manual correction of segmentation errors in all necessary B-scans. The automated analysis included in the AngioVue software allows quantitative assessment of the lesion area and flow inside the lesion. The upper left image shows the OCTA image of CNV at baseline, and the left lower image shows the structural OCT scan of CNV at baseline, showing the presence of subretinal fluid indicating CNV activity. The upper right image shows OCTA of CNV at the last visit, while the right lower image shows the structural OCT scan at the last visit showing a significant decrease of subretinal fluid, indicating a decrease of CNV activity

Table 1. Baseline demographics and ocular characteristics

Number of study subjects	**40**
Mean age, years	69 ± 5 years
Female, number	14
Hypertensive, number	19
Mean best corrected visual acuity	51.29 ± 14.8 ETDRS letters
Mean central retinal thickness, µm	476 ± 32 µm
CNV type 1, number	30
CNV type 2, number	10

Table 2. The mean area of choroidal neovascularization and mean flow area within the measured choroidal neovascularization at all follow-up visits

	Base line	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36
Area of CNV (mm2) (mean ±SD)	2.72 ± 4.29	2.61 ± 3.45	2.28 ± 3.11	2.01 ± 3.24	1.92 ± 3.18	1.84 ± 3.01	1.89 ± 2.76	1.52 ± 2.23	1.55 ± 1.94	1.41 ± 1.45	1.53 ± 1.07
Flow area within the measured CNV (mm2) (mean ±SD)	2.28 ± 2.08	1.92 ± 1.66	1.69 ± 1.48	1.46 ± 1.39	1.5 ± 1.37	1.3 ± 1.3	1.24 ± 1.28	1.32 ± 1.15	1.06 ± 1.05	0.99 ± 0.95	0.91 ± 0.63

4. DISCUSSION

In our study of the assessment of choroidal neovascular membrane by optical coherence tomography angiography (OCTA) after intravitreal anti-VEGF injection, we found a statistically significant decrease of CNV area, flow area within the measured CNV over the follow-up period.

The findings of our study are in line with other studies that evaluated choroidal neovascular membrane with anti-VEGF and showed a decrease of CNV size and CNV flow after treatement [11,12,13,14].

All these studies add to the fact that CNV area and flow area can be used as reliable parameters for following the activity of the CNV during treatment with anti-VEGF agents. On the other hand, it has been reported, using with fluorescein angiography, that the size of CNV remained stable after 1 year of anti-VEGF treatment [15].

The CNV size in fluorescein angiography is affected by leakage and pigment epithelial detachment. So, the two techniques complement each other as OCTA provides a convenient, noninvasive tool for documenting cross-sectional and three-dimensional displays with potential for projection artifacts and its inability to visualize low-flow lesions. In this study, we used the CNV area and flow area. CNV area reflects the overall change of the CNV and does not represent changes within the CNV itself.

In CNV, abnormal vessels from the CC grow underneath the RPE or the retina, leading to subretinal and/or intraretinal fluid. Consequently, SD-OCT is utilized for monitoring the activity by analyzing the fluid which represent a parameter of activity. In this OCT evaluation, only indirect parameters are drawn from changes in CNV. The decrease in the mathematical parameters (mean area and flow inside the CNV) during aflibercept treatment in this study may indicate the possibility of using this method as a second parameter for CNV activity [16].

This is in accordance with the previous studies that showed a reduction of peripheral small capillary vessels of the CNV during therapy. Reduction of the small peripheral vessels explain the decrease in area and flow inside the CNV [17,18].

Future larger studies will be able to compare the usefulness of these different quantitative metrics in monitoring CNV activity. However, FA and SD-OCT are still used to assess the CNV activity, OCTA is better than these modalities because it can detect vascular changes with treatment.

Our study has much strength due to its prospective design and presence of study protocol.

However, the study has some limitations due to the absence of comparing the effect of different commercially available anti-VEGF agents on the OCTA parameters of the choroidal neovascular membrane. Future studies, including a larger group of patients, might be able to compare these parameters between different drugs

5. CONCLUSION

Our study used OCTA to demonstrate a reduction in CNV area and flow area in response to intravitreal Aflibercept injection.

These findings demonstrate the valuable role of OCTA in diagnosis and follow-up of choroidal neovascular membrane activity during the course of therapy with anti-VEGF agents, and this is of high clinical significance as the OCTA is non-invasive modality so it is suitable for following up the CNV activity in each visit.

CONSENT AND ETHICAL APPROVAL

All patients were informed of the nature of the study and gave written informed consent before enrollment. The study was approved by the ethics committee of Tanta university.

The study was performed according to the principles of the Declaration of Helsinki. All subjects provided written informed consent to get involved in this study.

FINANCIAL DISCLOSURES

Ahmad R. Ziada (No financial disclosures), Mostafa Abd El Latif Abo El Einen (No financial disclosures), Hamdy Abd El Azim El Koumy (No financial disclosures), El Said Ibraheem El Dessouky (No financial disclosures).

AVAILABILITY OF MATERIALS AND DATA

The materials and data are available and can be requested from Ahmad R. Ziada, who is responsible for the data presented in this paper.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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