ROLE OF OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN ASSESSMENT OF AGE-RELATED NEOVASCULARIZATION RESPONSE TO INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR

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ABSTRACT

Introduction: Age-related macular degeneration (AMD) is a medical condition which may result in blurred or no vision in the center of the visual field. Early on there are often no symptoms. Spectral domain optical coherence tomography (SD-OCT) is a noninvasive imaging technique, able to visualize structural changes of the neuro sensory retina and the retinal pigment epithelium (RPE). Intravitreal injection is the standard method of administration, of antivascular endothelial growth factor Anti-VEGF which block its interaction with receptors on the endothelial cell surface and so retard or reverse vessel growth.

Aim: To relate choroidal neovascularization (CNV) area and CNV fine vascular pattern using Optical coherence tomography angiography (OCTA) and its response to intra vitreal anti - vascular endothelial growth factor (VEGF).

Methods: Our prospective quasi- experimental study was carried out on 30 eyes of patients with neovascular AMD at the Ophthalmic Outpatient Clinic at Suez Canal University Hospital, to monitor the response of CNV to Anti-VEGF to more efficient follow up and better visual outcome in this patient's category.

Results: There was highly statistically significant difference between different periods regarding both CNV area ($p<0.001$), and CNV fine vessel density ($p<0.001$). There was only statistically significant positive correlation between CNV area and type before ($r= 0.996$; $p< 0.001$), 48 hours ($r= 0.993$; $p < 0.001$).

Conclusion: OCT-A provides exact data on response CNV area after the anti VEGF treatment, it is a promising imaging modality that allows assessment of CNV fine vascular density response to anti VEGF, and it is a fast, non-invasive and reproducible method to study exudative AMD.

Key words: Macular Degeneration, Choroidal Neovascularization.

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Introduction

Age-related macular degeneration (AMD) is a degenerative disorder affecting the macula. It is characterized by the presence of specific clinical findings, including drusen and retinal pigment epithelium (RPE) changes, in the absence of another disorder. Later stages of the disease are associated with impairment of vision [(1)].

AMD can be classified into early and late phases. The early phase is characterized by large yellow subretinal deposits called drusen and RPE changes. The disease can progress to either choroidal neovascularization (CNV), a rapidly deteriorating late form of AMD characterized by new blood vessels that invade the macula, or to geographic atrophy GA, a slower late form causing degeneration of the macula's RPE [(2)].

WHO Lunched program called VISION 2020 which is a global initiative of the International Agency for the Prevention of Blindness (IAPB). The initiative seeks to eliminate the main causes of avoidable blindness in order to give all people in the world, particularly the millions of needlessly blind, the right to sight by the year 2020. Target disease areas for VISION 2020 include: Cataract, Refractive error, Trachoma, Childhood blindness, Onchocerciasis/river blindness, Glaucoma, Diabetic retinopathy, Age-related macular degeneration, Vitamin A deficiency [(3)].

Age-related macular degeneration is a major cause of blindness worldwide. With ageing populations in many countries, more than 20% might have the disorder [(4)].

Age-related macular degeneration AMD is the leading cause of severe and irreversible central visual loss in developed countries, affecting 10%–13% of adults over 65 years of age [(5)].

Risk factors for developing AMD are individuals aged more than 50 years, family history of AMD and history of smoking, individuals with this risk factors should undergo AMD screening on regular bases, to early detect the presence of choroidal neovascularization CNV in the setting of neovascular age related macular degeneration nAMD and give the appropriate treatment. Screening methods include visual acuity measurement and fundus examination, combined with self-monitoring Amsler grid [(6)].

In cases of suspected nAMD, further diagnostic testing should be performed, as fluorescein angiography FA, indocyanine green angiography ICGA, and optical coherence tomography OCT. FA provides anatomical details, detects the grade of activity, and plays a key role in the classification of the CNV [(7)].

The neovascular network of occult CNV is better identified by ICGA which useful also in the diagnosis of two other specific forms of nAMD, retinal angiomatous proliferation RAP and polypoidal choroidal vasculopathy PCV, characterized by lower incidence, more aggressive natural history, and poorer response to antiangiogenic therapy [(8,9)].

Spectral domain optical coherence tomography (SD-OCT) is a noninvasive imaging technique, able to visualize structural changes of the neuro sensory retina and the retinal pigment epithelium RPE. OCT is used to support the initial diagnosis of CNV obtained from FA and ICGA and to detect early signs of CNV activity, such as subretinal fluid, intraretinal cystoid spaces, and pigment epithelium detachment PED [(10,11)].

Recently, optical coherence tomography angiography (OCTA) has been introduced in clinical practice. OCTA provides cross-sectional and three-dimensional imaging of the retinal and choroidal vasculature with micrometer scale depth resolution [(12,13)].

Intravitreal injection is the standard method of administration, of antivascular endothelial growth factor Anti-VEGF which block its interaction with receptors on the endothelial cell surface and so retard or reverse vessel growth. They have become the predominant means of treatment for CNV, dramatically improving the visual prognosis [(1)].

Ranibizumab is a humanized monoclonal antibody fragment developed specifically for use in the eye, though is derived from the same parent mouse antibody as bevacizumab. It non-selectively binds and inhibits all isoforms of VEGF-A. The usual dose is 0.5 mg in 0.05 ml. Three initial monthly injections followed by monthly review with re-injection when deterioration occurs as assessed by VA (e.g. loss of 5 letters or more) and OCT (e.g. retinal thickness increase of 100 μm or more) [(2)].

The potential role of OCTA as first noninvasive diagnosis of nAMD, combined with or without gold-standard dye angiographic techniques, still objects of debate. Our rational in this study is frequent patients presented to us at ophthalmology outpatient clinic at Suez Canal University Hospital with nAMD, so treatment response to Anti-VEGF will be assessed at these patients using OCT-A.

Aim of the work: To relate CNV area and CNV fine vascular pattern using OCTA and its response to intra vitreal anti -VEGF.

Patients and Methods

This quasi- experimental study was conducted at the Ophthalmic Outpatient Clinic at Suez Canal University Hospital on patients with neovascular age-related macular degeneration after fulfilling the inclusion criteria.

Inclusion criteria:

Patients were enrolled in this study if they fulfill all of the following criteria:

- ✓ 1.Age group: 5o years and above.
- ✓ Both sexes.
- ✓ Established diagnosis of AMD neovascularization using fluorescein angiography and spectral domain OCT.
- ✓ Only clear identification of the morphology and extent of neovascularization on OCTA were enrolled in this study.

Exclusion criteria:

Patients were excluded from the study if they had any of the following criteria.

- ✓ The presence of any significant media opacity could affect image quality.
- ✓ Patients with history or clinical evidence of diabetic retinopathy. 65
- ✓ Myopia greater than 6 diopters.
- ✓ Glaucoma and other hereditary, inflammatory and/or vascular chorio retinal diseases not directly related to AMD.
- ✓ Pervious retinal laser treatment.

Based on previous study [(14)] in which the mean CNV size two days after injection of anti-VEGF was 297.50, the mean baseline CNV size was330.25 μm, and the estimate of the standard deviation was 0.0692. By sample size calculation, the sample size was equal to 25 eyes. 20% drop out percentage was calculated, so sample size was 30 eyes.

Data collection

(A) Base line assessment:

Patients were diagnosed with active AMD neovascularization by clinical examination and confirmed by fundus fluorescein angiography (FFA) and OCT were assessed as following:

1. History taking include:

- ✓ Personal data: name, age, sex, residency, telephone number and occupation.
- ✓ Data related to exclusion criteria.

✓ Data related to medical condition and current medications used.
✓ Duration of disease, defined as the time between the first diagnosis of CNV and a number of eventually prior anti-VEGF treatments were obtained from medical records.

2. Complete ocular examination*:*

✓ Visual acuity assessment: unaided and aided using Landolt (C) chart.
✓ Refraction: autorefractometer.
✓ External examination: lids, lashes, lacrimal apparatus and orbit.
✓ Examination of ocular alignment and motility.
✓ Assessment of pupillary function.
✓ Intra-ocular pressure measurement: using Goldman applanation tonometer.
✓ Slit-Lamp biomicroscopic examination.
✓ Dilated examination: of the lens, macula (by Volk's non-contact double aspheric biconvex lens (power: +90D), peripheral retina - (by Indirect ophthalmoscope), optic nerve and vitreous.

3. OCT angiography imaging:

A large pupil and clear media were ensured for accurate measurement.

(B) Image Acquisition for OCT-A for initial and follow up visits:

OCT images were obtained using a swept source OCT device (Topcon, Tokyo Japan), with the split-spectrum amplitude-decorrelation angiography algorithm. The device was operated with a central wavelength of 1040 nm, an acquisition speed of 70,000 A-scans per second, and a bandwidth of 45 nm. The size of scan ranges from 3x3 up to 6x6 according to size of CNV membrane.

Automatic segmentation was performed by the viewing software to generate enface projection images of the NV lesion.

Manual segmentation: In the event of segmentation errors, the thickness between the two segmentation lines were manually adjusted to include the whole NV complex.

During follow-up examinations, both OCTA scans were taken using the follow-up tracing mode, ensuring identification of previous scanned locations and allowing the evaluation of the same area.

(C) OCTA Image analysis at initial and follow up visits: OCTA image analysis:

1. For quantitative analysis: CNV area was measured by manually outlining CNV borders, using the drawing tool provided by the OCTA software. The automated software provided the correspondent value in square micrometer. The measure was performed at the enface baseline OCTA image and at both follow-up images.

2. For qualitative analysis: the density of CNV fine vessels changes were assessed and Qualitative analysis of OCTA outer retina choriocapillaris (ORCC) segmentation images at baseline and at each follow-up visit was consisted in morphological criteria from recent literature [15,16].

Both qualitative and quantitative parameters of OCTA were independently analyzed by two well-trained masked operators, in a random and masked fashion both to clinical and to OCT or OCTA findings. For qualitative parameters, in case of disagreement, arbitration was given by a retinal specialist.

(D) Follow up visits:

Duration: A regular follow-up visit with repeat OCTA after treatment with anti-VEGF therapy 2 days after injection and one week after injection.

For follow-up examination: Two different enface OCTA images were analyzed using two different slabs, in order to evaluate, if possible, thickness changes of both choroid and neovascular lesion could interfere with OCTA enface analysis of CNV area at follow-up. The first one was obtained using the same baseline thickness slab independently to the eventual new location of the sclerochoroidal interface; the second one was obtained by rearranging the deeper segmentation line at the sclerochoroidal interface.

Data management

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). The significance of the obtained results was judged at the 5% level.

1 - ANOVA with repeated measures: for normally distributed quantitative variables, to compare between more than two periods or stages, and Post Hoc test (Bonferroni adjusted) for pairwise comparisons.

2 - Friedman test: For abnormally distributed quantitative variables, to compare between more than two periods or stages and Post Hoc Test (Dunn's) for pairwise comparisons.

Results

Table 1 showed that 17 (56.7%) of participants were females while 13 (43.3%) were males. More than half of participants 17 (56.7%) were >60, while 13 (43.3%) were ≤60 years old. The mean age (61.83 ± 3.50 years) ranged from 55 to 67 years, more than half of participants 18 (58.1%), while 13 (41.9%) participants were type 2.

Table 2 showed that there was highly statistically significant difference between different periods regarding CNV area ($p<0.001$).

Table 3 demonstrated that there was highly statistically significant difference between different periods regarding CNV fine vessel density ($p<0.001$).

Table 4 demonstrated that no statistically significant correlation was found between the different periods of CNV fine vessel density and age, type, area before, area 48 hours, or area 1 week.
Table 5 demonstrated that no statistically significant correlation was found between CNV type and age.

Table 6 demonstrated that there was only statistically significant positive correlation between CNV area and type before (r= 0.996; p< 0.001), 48 hours (r= 0.993; p < 0.001).

Table (1): Distribution of the studied cases according to demographic data (n = 30).

Demographic data	No.	%
Sex		
Male	13	43.3
Female	17	56.7
Age (years)		
≤60	13	43.3
>60	17	56.7
Mean ± SD.	61.83 ± 3.50	
Median (IQR)	61.50 (59.0 – 65.0)	
CNV type		
I	13	41.9
II	18	58.1

IQR: **Inter quartile range** SD: **Standard deviation**

Table (2). Comparison between the different periods according to CNV area (n = 30).

CNV area	Before	After		F	p
		48 hours	1 week		
Mean ± SD.	3.39 ± 1.05	3.22 ± 1.02	3.04 ± 0.99	157.726*	<0.001*
Median (IQR)	3.50 (2.60 – 4.1)	3.35 (2.4 – 3.8)	3.15 (2.3 – 3.50)		
Sig. bet. Grps	p_1<0.001*, p_2<0.001*, p_3<0.001*				

F: F test (ANOVA) with repeated measures, Sig. bet. periods was done using **Post Hoc Test** (**adjusted Bonferroni)**
p_1: p value for comparing between **before** and **after 48 hour**
p_2: p value for comparing between **before** and **after 1week**
p_3: p value for comparing between **after 48 hour** and **1 week**
*: Statistically significant at p ≤ 0.05

Table (3). Comparison between the different periods according to CNV fine vessel density.

CNV fine vessel density	Before		After				Fr	p
			48 hours		1 week			
	No.	%	No.	%	No.	%		
Present	30	100.0	0	0.0	0	0.0	60.0*	<0.001*
Decreased	0	0.0	22	73.3	22	73.3		
Increased	0	0.0	0	0.0	0	0.0		
Stable	0	0.0	8	26.7	8	26.7		
Sig. bet. Grps	p_1<0.001*, p_2<0.001*, p_3=1.000							

Fr: **Friedman test**, Sig. bet. periods were done using **Post Hoc Test** (**Dunn's)**
p: p value for comparing between the studied periods
p_1: p value for comparing between **before** and **after 48 hour**
p_2: p value for comparing between **before** and **after 1week**
p_3: p value for comparing between **after 48 hour** and **1 week**
*: Statistically significant at p ≤ 0.05

Table (4). Correlation between the different periods of CNV fine vessel density and other studied variables.

CNV fine vessel density		Correlation coefficient	p
Age	**Before**	0.066	0.730
	48 hours	0.085	0.655
	1 week	0.090	0.637
Type	**Before**	-0.212	0.245
	48 hours	0.223	0.222
	1 week	0.223	0.222
Area Before	**Before**	0.002	0.990
	48 hours	-0.003	0.987
	1 week	0.011	0.955
Area 48 hours	**Before**	0.233	0.215
	48 hours	0.232	0.218
	1 week	0.245	0.192
Area 1 week	**Before**	0.233	0.215
	48 hours	0.232	0.218
	1 week	0.245	0.192

Table (5). Correlation between CNV type and age.

CNV Type	Correlation coefficient	p
I	-0.251	0.182
II	0.251	0.182

Table (6). Correlation between the different periods of CNV area and other studied variables.

CNV area		Correlation coefficient	p
Age	**Before**	0.066	0.730
	48 hours	0.085	0.655
	1 week	0.090	0.637
Type	**Before**	0.996	< 0.001
	48 hours	0.993	< 0.001
	1 week	-0.238	0.205
fine vessel density Before	**Before**	0.002	0.990
	48 hours	-0.003	0.987
	1 week	0.011	0.955
fine vessel density 48 hours	**Before**	0.233	0.215
	48 hours	0.232	0.218
	1 week	0.245	0.192
fine vessel density 1 week	**Before**	0.233	0.215
	48 hours	0.232	0.218
	1 week	0.245	0.192

Discussion

Intravitreal anti- VEGF therapy is the gold standard for treating neovascular age-related macular degeneration treatment [(17)].

CNV plays a key role in the pathogenesis of AMD. Classically, fluorescein angiography is the gold standard for diagnosing CNV. However, intravenous fluorescein injection is known to have various side effects, ranging from nausea to anaphylaxis [(18)].

Thus, with the advent of OCTA, choroidal vasculature can be non-invasively visualized with high resolution, allowing greater insight into choroidal vascular disorders. Using OCTA, CNV can be detected with no injection of any dye and their changes may be appreciated during follow-up [(19)].

So, this study was carried out to use OCTA to monitor the response of choroidal neovasculaization CNV to Anti-VEGF to more efficient follow up and better visual outcome in this patient's category.

Our study results have revealed that 56.7% of cases were females while only 43.3% were males. Similarly, it was found that neovascular AMD is more common in women compared with men in Western populations [(20)], while conversely, Asian women have much lower prevalence of neovascular

AMD, approximately 1/3, compared with Asian men [21].

Some studies have presented that differential risk associations exist for AMD between men and women. Among these risk factors are waist circumference, body mass index (BMI), systolic blood pressure (SBP), physical exercise, and coronary artery disease [22].

These studies suggest that AMD disease development might follow different processes in men and women. Further support arises from observations of an association between younger age at menarche and decreased risk for AMD and a protective effect of hormone therapies against the development of AMD in women [23].

In our study, the mean age of our study participants was (61.83 ± 3.50 years). This could be explained by that ARMD risk increases with age, and the risk increases more than three-fold in patients older than 75 years of age compared to the group of patients between 65-74 years of age (Beaver Dam Eye Study; Framingham Eye Study) [24].

In this study, there was a statistically significant decrease in the mean CNV area 48 hours and 1 week after treatment. An earlier reduction, at 24 hours of type 2 CNV area at OCTA has also been recently observed in five eyes by Lumbroso et al. [25].

Similarly, VIEW 1 and 2 showed an average decrease in CNV area after one year, but this decrease was very small with approximately 4% in all treatment groups [26].

Also, McClintic et al. [27] followed up patients on PRN antiVEGF therapy with quantitative OCT-A, measured CNV vessel area and membrane area, which reduced after three months, as compared to baseline.

And Miere et al. [28] found that the final OCTA images revealed a decrease in CNV total area of 21.6%, in 6/17 eyes, the baseline neovascular pattern was unchanged; these cases were associated with exudation at the final spectral domain OCT examination and a decrease in CNV area of 34.1%. Conversely, in 64.7% of cases, the initial pattern had changed to a pruned vascular tree pattern, with variable exudative status on spectral domain OCT at the final visit and a decrease in total CNV area of 0.07%. These findings suggest that vessel area could provide important information on the therapeutic response to anti-VEGF, as immediate vascular constriction has been shown as a typical reaction to VEGF blockade [26].

However, Mastropasqua et al. [29] detected no reduction of type 1 CNV area at OCTA 24 hours after aflibercept injection in 15 naïve eyes. Moreover, they observed no reduction of the central retinal thickness.

Also, Kuehlewein et al. [30] found no CNV area change after three months of follow-up in patients with active or chronic type 1 neovascularization, which is most likely due to the chronicity of most of the lesions included in their study.

In contrast to our results, large-scale studies such as the CATT [31], and ANCHOR [32] trials showed an increase in CNV area while under continuous anti-VEGF treatment or in the sham group using fundus photography and fluorescein angiography. These different findings may be explained by the too short interval after treatment.

In the current study, CNV vessel density was assessed subjectively by assessment CNV vessel density before, after 48 hours and 1 week post anti VEGF injection. There was a statistically significant decrease of the CNV fine vessel density after 48 h and 1 week of anti-VEGF treatment, it was decreased in 73.3% and remained stable in 26.7% of cases after 48 hours and 1 week after treatment. This was in line with Muakkassa et al. [33] who reported that the anti-VEGF therapy seems to induce a quantitative regression with a variable decrease in size and vessel density of the neovascular membrane, which has been described from 2 to 9.5 weeks after treatment.

Similarly, Resch et al. [24] data suggests that after one year of anti VEGF treatment, reduced vessel density in three of the four examined vascular regions can be found independent of the treatment regimen. There are some hypotheses that could explain the decreased vascular density in patients with treated nAMD. Anti-VEGF therapy may promote decreased vascular density by counteracting the role of constitutively produced VEGF in neuronal or vascular maintenance. Also, that the decreased vascular density may be secondary to RPE deterioration because the RPE produces and secretes a variety of growth factors, including VEGF, which play a role in maintaining the CC. RPE cells secrete VEGF toward the CC, and VEGF receptors in humans are expressed on the choroidal endothelium facing the RPE layer, atrophy is ubiquitous in late stage nAMD, and may accelerate the decreased vascular density in the CC. Another hypothesis is secondary to the exudative changes themselves; episodic leakage over a period of years that subject the macula to serous fluid and blood, mechanical damage from CNV outgrowth and contraction, and ischemic and inflammatory effects should be considered [34].

The study also has its strengths. It was designed prospectively, and quantitative changes in CNV flow patterns were tracked over time while under a strict protocol of anti-VEGF treatment. Great care was taken to ensure that quantitative OCTA metrics were as accurate as possible by applying manual segmentation correction, reducing the impact of artifacts, and evaluating the within-visit repeatability to reduce the chance that observed changes were the result of expected scan-to scan variation. However, our study had some limitations. First is the small sample size. However, this was a

short prospective study (less than 2 months long) in which all patients, undergoing intravitreal injection for exudative AMD, were consecutively enrolled. Second, the short follow-up period did not allow to analyse late choroidal changes. Also, the limits which are related to technical limitations of OCTA technology. Finally, we didn't evaluate each CNV type separately, though that the type of CNV is a factor that determines the natural progression of the disease.

Conclusion

OCT-A provides exact data on response CNV area after the anti VEGF treatment, it is a promising imaging modality that allows assessment of CNV fine vascular density response to anti VEGF, and it is a fast, non-invasive and reproducible method to study exudative AMD. By means of this technique, we were able to find early changes in the structure and size of CNV, independently to the duration of disease. Optical coherence tomography angiography thus highlights the strengths and weaknesses of current therapies for AMD. OCTA helps to understand the pathophysiological implications of neovascular AMD. OCTA allows to monitor disease progression in treated eyes with anti VEGF and this information can be used to compare treatment response directly between different CNV types.

Recommendations

✓ Larger studies are needed to validate if the different CNV subtypes based on OCTA can be predictive of unique treatment response with anti-VEGF therapy.

✓ Prospective studies are required to highlight the fine changes in retinal vascular changes exactly.

✓ Future studies are needed to follow these treatment patients over the course of their treatment. At this time, what happens to these lesions with repeated treatment is unclear.

✓ As few studies have analyzed OCTA images in patients undergoing treatment with anti-VEGF agents; however, these studies did not include longitudinal assessment from initiation of treatment. Future studies should follow these lesions longitudinally to describe the OCTA findings of treated CNV over time.

✓ At this time, the only medications to treat abnormal vascularization of the choroid and retina are anti-VEGF agents that work as antiangiogenic medications. In the future, as medications that target vascular remodeling enter clinical trials, OCTA may be a valuable tool in assessing how CNVs respond differently to these agents as compared with anti-VEGF agents.

Conflict of interest statement

The authors affirm that they do not have any competing interests.

Ethical approval

✓ Patients were informed about the study and its objectives.

✓ The steps of the study, its potential benefits and risks were discussed with each individual patient.

✓ Complications arising from injection or imaging procedure were managed accordingly.

✓ The patients were notified about the clinical examination and follow up visits.

✓ To ensure data confidentiality, a code number addressed each patient for contact and follow up.

✓ Each patient was offered the proper management accordingly.

✓ None of the patients' data was distributed outside the field of medical research and every effort was done to preserve patient's privacy and dignity.

✓ Patients who were not comply with the follow up were canceled of the study.

Authors contribution

All authors are equally contributed.

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