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Age-related Neovascularization Response to Intravitreal Anti-vascular Endothelial Growth Factor

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Abstract

Background: **A medical disorder called age-related macular degeneration (AMD) can cause impaired or absent vision in the center of the visual field. Initially, there are frequently no symptoms. A non-invasive imaging method called Spectral Domain Optical Coherence Tomography (SD-OCT) can show structural alterations in the retinal pigment epithelium (RPE) and neurosensory retina. Anti-vascular endothelial growth factor Anti-VEGF is often administered intravitreally to slow or stop the formation of blood vessels by blocking its interaction with receptors on the surface of endothelial cells.** ***Aim:*** **To describe changes in age-related choroidal neovascularization CNV to intravitreal anti-VEGF using OCTA.** ***Methods:*** **We conducted a prospective quasi-experimental study on 30 eyes of patients with neovascular AMD at the Suez Canal University Hospital's Ophthalmic Outpatient Clinic to observe how CNV responded to anti-VEGF for improved visual results and more effective follow-up in this patient group.** ***Results:*** **There was a highly statistically significant difference between different periods regarding both CNV area ($p<0.001$), and CNV fine vessel density ($p<0.001$).** ***Conclusion:*** **OCT-A is a quick, non-invasive, and repeatable way to examine exudative AMD. It offers precise data on the region of the CNV that responds to anti-VEGF treatment, and it is a promising imaging technique that permits assessment of the CNV fine vascular density response to anti-VEGF.**

Keywords Macular Degeneration, Optical Coherence Tomography

Introduction

The macula is impacted by age-related macular degeneration (AMD), a degenerative condition. The absence of another condition is accompanied by the presence of certain clinical symptoms, such as drusen and alterations in the retinal pigment epithelium (RPE). The disease's latter stages are linked to eyesight impairment[1]. There are two stages of AMD: early and late. Large yellow subretinal deposits known as drusen and RPE alterations define the early stages. Geographic atrophy GA, a slower late type of AMD that results in RPE degradation in the macula, or choroidal neovascularization (CNV), a quickly deteriorating late form of AMD, are both possible outcomes as the condition advances[2]. The International Agency

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for the Prevention of Blindness (IAPB), a worldwide effort, launched a program dubbed VISION 2020 during a luncheon hosted by the WHO. The program aims to end the primary causes of preventable blindness by the year 2020, granting everyone around the globe, especially the millions of unnecessarily blind people, the right to sight. Cataract, refractive error, trachoma, childhood blindness, onchocerciasis/river blindness, glaucoma, diabetic retinopathy, age-related macular degeneration, and vitamin A insufficiency are among the diseases that VISION 2020 is aiming to treat [3]. Globally, age-related macular degeneration is a major factor in blindness. Given the aging population in many nations, the condition might affect more than 20% of people[4]. Affecting 10%–13% of persons over 65, AMD is the most common cause of severe and permanent central vision loss in developed nations[5]. Age over 50, a family history of AMD, and a history of smoking are risk factors for developing AMD. People with these risk factors should regularly undergo AMD screening to detect choroidal neovascularization CNV early in the course of neovascular age-related macular degeneration (nAMD) and provide the necessary treatment. Visual acuity testing and fundus examination are screening techniques that are paired with self-monitoring Amsler grid[6]. Further diagnostic testing, including fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT), should be carried out in patients with suspected nAMD. FA gives anatomical information, determines the level of activity, and is crucial in classifying the CNV[7]. The ICGA is more effective at identifying the neovascular network of occult CNV and is also helpful in the diagnosis of two other distinct types of nAMD, retinal angiomatous proliferation RAP and polypoidal choroidal vasculopathy PCV, which have a lower incidence, a more aggressive natural history, and a worse response to antiangiogenic therapy[8,9]. A non-invasive imaging method called Spectral Domain Optical Coherence Tomography (SD-OCT) can show structural changes in the retina's neurosensory layer and retinal pigment epithelium (RPE). OCT is utilized to corroborate the initial CNV diagnosis made by FA and ICGA as well as to identify the earliest indications of CNV activity, such as subretinal fluid, intraretinal cystoid gaps, and pigment epithelium detachment PED[10,11]. Optical coherence tomography angiography (OCTA) has just recently been adopted in clinical settings. With micrometer scale depth resolution, OCTA offers cross-sectional and three-dimensional imaging of the retinal and choroidal vasculature[12,13]. The most common way to provide antivascular endothelial growth factor (Anti-VEGF), which inhibits its interaction with receptors on the surface of endothelial cells and hence slows or stops vessel development, is by intravitreal injection. They are now the main form of CNV therapy, greatly enhancing the prognosis for visual impairment[1]. Developed particularly for use in the eye, ranibizumab is a humanized monoclonal antibody fragment that comes from the same parent mouse as bevacizumab. All VEGF-A isoforms are non-selectively bound to and inhibited by it. A dosage of 0.5 mg in 0.05 ml is customary. as degeneration is detected by VA (e.g., loss of 5 letters or more) and OCT (e.g., rise in retinal thickness of 100 µm or more), there are three initial monthly injections, followed by a monthly evaluation and re-injection as necessary[2]. The prospective use of OCTA in conjunction with or without gold-standard dye angiograph-

ic methods as the initial noninvasive diagnosis of nAMD is still up for dispute. Our justification for this study is that we frequently see patients with nAMD at the Suez Canal University Hospital's ophthalmology outpatient clinic. We will use OCT-A to evaluate these patients' responses to anti-VEGF therapy. This study aimed to describe changes in age-related choroidal neovascularization CNV to intravitreal anti-VEGF using OCTA.

Patients and Methods

Patients who met the inclusion criteria for this quasi-experimental study with neovascular age-related macular degeneration were treated at the Suez Canal University Hospital's Ophthalmic Outpatient Clinic. Patients 50 years and above of both genders with a confirmed diagnosis of AMD neovascularization utilizing spectral domain OCT and fluorescein angiography were included. Only subjects with a thorough understanding of the shape and degree of neovascularization on OCTA were included. We excluded 1) Patients with any significant media opacity that could affect image quality. 2) History or clinical evidence of diabetic retinopathy. 3) Myopia is greater than 6 diopters. 4) Glaucoma and other hereditary, inflammatory, and/or vascular chorio retinal diseases not directly related to AMD. Or 5) Previous retinal laser treatment. Based on a previous study[14] in which the mean CNV size two days after injection of anti-VEGF was 297.50, the mean baseline CNV size was 330.25 µm, and the estimate of the standard deviation was 0.0692. By calculation, the sample size was equal to 25 eyes. A 20% dropout percentage was calculated, so the sample size was 30 eyes.

Data collection
(A) Baseline assessment:

Patients who had active AMD neovascularization determined by clinical examination, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT), were rated as follows:
1. History taking: Personal data: name, age, sex, residency, telephone number, and occupation. Data related to exclusion criteria. Data related to medical conditions and current medications used. Medical records were used to determine the length of the illness, which was calculated as the interval between the initial CNV diagnosis and any earlier anti-VEGF therapy.

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. Intraocular pressure measurement: using Goldman application tonometer. Slit-Lamp biomicroscopic examination. Dilated examination of the lens, macula, optic nerve, vitreous, and peripheral retina with an indirect ophthalmoscope and Volk's non-contact double aspheric biconvex lens (power: +90D).

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:
Using a sweeping source OCT device (Topcon, Tokyo, Japan) and the split-spectrum amplitude-decorrelation angiography method, OCT pictures were produced. The system was run using a 1040 nm central wavelength, 70,000 A-scans per second acquisition speed, and a 45 nm bandwidth. Depending on the size of the CNV membrane, the size of the scan might

range from 3x3 to 6x6. The viewing program automatically segmented the NV lesion to provide enface projection pictures of it. Segmentation faults were handled manually by adjusting the thickness between the two segmentation lines to take the whole NV complex into account. Both OCTA scans were performed utilizing the follow-up tracing mode during follow-up exams, guaranteeing the recognition of previously scanned regions, and enabling the evaluation of the same region.

(C) OCTA Image analysis at initial and follow-up visits: OCTA image analysis:
1. For quantitative analysis: Using the drawing tool offered by the OCTA program, the CNV area was measured by manually delineating the CNV boundaries. The corresponding square micrometer value was supplied by the automated program. The measurement was carried out at both the follow-up pictures as well as the baseline enface OCTA image.
2. For qualitative analysis: Alterations in the density of CNV fine vessels were evaluated and Morphological criteria from current literature were used for the qualitative analysis of OCTA outer retina choriocapillaris (ORCC) segmentation pictures at baseline and at each follow-up visit[15,16]. Two skilled masked operators separately examined the qualitative and quantitative OCTA parameters in a random and masked manner concerning the clinical and OCTA or OCT results. In the event of a dispute about the qualitative standards, a retinal expert provided arbitration.

(D) Follow-up visits
Duration: A routine follow-up with a second OCTA following anti-VEGF therapy 2 days and 1 week after injection.
*Follow-up examination***:** To assess, if possible, thickness variations of both the choroid and the neovascular lesion that may interfere with OCTA enface analysis of the CNV region during follow-up, two separate enface OCTA pictures were analyzed using two different slabs. The first one was created by moving the deeper segmentation line at the sclerochoroidal interface, whereas the second one was created by employing the same baseline thickness slab independently to the final new position of the sclerochoroidal interface.

Data Analysis

With the aid of the IBM SPSS software package version 20.0, data was input into the computer for analysis. (IBM Corp, Armonk, NY). The Shapiro-Wilk test was performed to evaluate if the distribution was normal, and percentages and figures were employed to summarize the qualitative data. The range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) were used to characterize quantitative data. The 5% level was used to determine the significance of the obtained data. ANOVA with repeated measures to compare more than two periods or stages for normally distributed quantitative variables, and the Post Hoc test (Bonferroni adjusted) for pairwise comparisons. Friedman's test compares more than two periods or stages for quantitative variables with anomalous distributions and uses the Post Hoc Test (Dunn's) for pairwise comparisons.

Results

Table 1 showed that 17 (56.7%) of the participants were females while 13 (43.3%) were males. More than half of the participants 17 (56.7%) were >60, while 13 (43.3%) were ≤60 years old. The mean age was (61.83 ± 3.50 years) ranging from 55 to 67

years. Table 2 showed that more than half of participants 18 (58.1%), while 13 (41.9%) participants were type 2. Table 3 showed that there was a highly statistically significant difference between different periods regarding the CNV area (p<0.001). Table 4 demonstrated that there was a highly statistically significant difference between different periods regarding CNV fine vessel density (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)	

IQR: Inter quartile range, SD: Standard deviation

Discussion

The gold standard for treating neovascular age-related macular degeneration is intravitreal anti-VEGF therapy[17]. The pathogenesis of AMD is heavily reliant on CNV. For diagnosing CNV traditionally, fluorescein angiography has been the gold standard. However, there are several negative effects associated with intravenous fluorescein injection, from nausea to allergy[18]. As a result, the development of OCTA has made it possible to non-invasively and accurately visualize the choroidal vasculature, giving researchers a better understanding of choroidal vascular diseases. Without injecting any dye, OCTA may identify CNV and any alterations can be seen during follow-up[19]. Therefore, this study was conducted to follow up more effectively and improve the visual result in this patient's category by using OCTA to assess the response of choroidal neovascularization CNV to anti-VEGF. According to the findings of our study, there were 56.7% more female instances than male cases—only 43.3%.

Table 2: CNV type (n = 30).

Type	No.	%
1	13	41.9
2	18	58.1

Similarly, it was found that neovascular AMD is more common in women compared with men in Western populations[20], while conversely, Asian women have a much lower prevalence of neovascular AMD, approximately 1/3, compared with Asian men[21]. According to several research, males and women have distinct risk connections for AMD. Waist circumference, body mass index (BMI), systolic blood pressure (SBP), exercise, and coronary artery disease are some of these risk factors[22]. According to these findings, men and women may experience AMD disease progression in ways that are distinct from one another. Additional evidence for this claim comes from studies showing a link between menarche at a younger age and a lower incidence of AMD as well as a protective role for hormone therapy in preventing AMD in female patients[23]. The average age of the participants was (61.83 ± 3.50 years). According to the Beaver Dam Eye Study and the Framingham Eye Study, the risk of developing ARMD rises with age and is more than three times higher in patients over 75 than it is in individuals between 65 and 74[24]. The mean CNV area in this research decreased statistically significantly 48 and 1 week after therapy. Also Lumbroso et al.[25] noted in five eyes, an early decrease of type 2 CNV area at OCTA at 24 hours. Similar to VIEW 1, VIEW 2 also demonstrated an average reduction in CNV area after a year, however, this reduction was only 4% across all treatment groups[26].

Table 3: 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 were 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 1 week.
p_3: p-value for comparing between after 48 hours and 1 week.
**: Statistically significant at p ≤ 0.05*

Table (4). 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 hours.
p_2: p-value for comparing between before and after 1 week.
p_3: p value for comparing between after 48 hour and 1 week.
**: Statistically significant at p ≤ 0.05*

Also, in McClintic et al.[27] study, quantitative OCT-A was used to monitor patients receiving PRN anti-VEGF medication, measuring the area of the CNV vessel and membrane after three months compared to the baseline. Miere et al. [28] observed that the baseline neovascular pattern was unaltered in 6/17 eyes and that the final OCTA pictures showed a drop in CNV total area of 21.6%. These instances were connected to exudation at the final spectral domain OCT examination and a decrease in CNV area of 34.1%. On the other hand, the initial pattern had transformed in 64.7% of instances to a trimmed vascular tree pattern, with varied exudative status on spectral domain OCT at the last visit and a reduction in overall CNV area of 0.07%. Considering that rapid vascular constriction has been demonstrated to be a common response to VEGF blockage, our findings imply that the vessel area might give crucial information on the therapeutic response to anti-VEGF[26]. Mastropasqua et al.[29] could not find any decrease in the type 1 CNV region at OCTA 24 hours after injecting aflibercept into 15 untrained eyes, nevertheless. They also saw no decrease in the central retinal thickness. Additionally, Kuehlewein et al.[30] reported no CNV area changes in patients with active or chronic type 1 neovascularization after three months of follow-up, which is most likely because the majority of the lesions included in their analysis were chronic. In contrast to our results, large-scale studies such as the CATT [31], and ANCHOR[32] trials Using fun-

dus photography and fluorescein angiography, it was demonstrated that CNV area increased while receiving continuous anti-VEGF medication in the control group. The short period following therapy may be the cause of these varied outcomes. In the current investigation, CNV vessel density was evaluated subjectively by measuring it before, 48 hours after, and one week after receiving an anti-VEGF injection. After 48 hours and one week of anti-VEGF therapy, there was a statistically significant reduction in the CNV fine vessel density; it was reduced in 73.3% of instances and stayed steady in 26.7% of cases. This was in line with Muakkassa et al.[33] who showed that between 2 to 9.5 weeks following treatment, anti-VEGF medication appears to cause a quantitative regression with a varied decrease in the size and vessel density of the neovascular membrane. In a similar vein, evidence from Resch et al.[24] shows that lower vessel density in three of the four investigated vascular locations can be seen after one year of anti-VEGF treatment, regardless of the treatment protocol. There are a few theories that might explain why people with treated nAMD have less blood vessel density. By preventing constitutively generated VEGF from maintaining neurons or blood vessels, anti-VEGF treatment may lead to reduced vascular density. Deterioration of the RPE may also be a contributing factor to the reduced vascular density, since the RPE generates and secretes several growth factors, including VEGF, which are important for maintaining the CC. Atrophy is common in late-stage nAMD and may hasten the decline in vascular density in the CC. RPE cells produce VEGF towards the CC, and VEGF receptors are found on the choroidal endothelium confronting the RPE layer in humans. In addition to the exudative alterations themselves, it is important to consider episodic leaking throughout the time that exposes the macula to blood and serous fluid, mechanical harm from CNV expansion and contraction, and ischemia and inflammatory consequences[34]. Studying does have some advantages. It was created prospectively, and while adhering to a stringent anti-VEGF therapy procedure, quantifiable changes in CNV flow patterns were monitored over time. By applying manual segmentation correction, minimizing the impact of artifacts, and assessing the within-visit repeatability, great care was taken to ensure that quantitative OCTA metrics were as accurate as possible. This decreased the likelihood that observed changes were the result of anticipated scan-to-scan variation. Our study, however, had certain drawbacks. The tiny sample size comes first. However, all patients receiving intravitreal injections for exudative AMD were sequentially recruited in this brief prospective research (less than 2 months in length). Second, the brief follow-up time frame prevented analysis of late choroidal alterations. Additionally, there are restrictions connected to OCTA technology's technical restrictions. Finally, even though the type of CNV is a determinant that dictates the natural development of the illness, we did not assess each CNV type independently.

Conclusion

OCT-A is a quick, non-invasive, and repeatable way to examine exudative AMD. It gives precise data on the response CNV region following anti-VEGF treatment and is a promising imaging technology that allows assessment of CNV fine vascular density response to anti-VEGF.

Recommendations

Larger investigations are required to con-

firm if the various CNV subtypes determined by OCTA may predict the individual treatment response to anti-VEGF medication. To precisely emphasize the subtle variations in retinal vascular alterations, prospective investigations are needed. Future research is required to monitor these people while they get therapy. It is yet unknown what will happen to these lesions after repeated therapy. A small number of studies have examined OCTA pictures in patients using anti-VEGF medications, however these investigations omitted longitudinal monitoring from the start of therapy. Future research should monitor these lesions over time to characterize changes in the treated CNV's OCTA results. Currently, only anti-VEGF therapies that also act as antiangiogenic drugs may treat aberrant vascularization of the choroid and retina. As drugs that target vascular remodeling reach clinical trials in the future, OCTA may prove to be a useful tool in determining how CNVs react differently to these drugs in comparison to anti-VEGF therapies.

Conflict of interest statement

The writers declare that their interests are not at odds with one another.

Ethical approval

Patients received information regarding the study's goals. Each patient was given a detailed explanation of the study's procedures, prospective advantages, and hazards. Injection-related or imaging-related complications were treated appropriately. The clinical assessment and subsequent visits were informed to the patients. Each patient was assigned a code number for contact and follow-up to protect the confidentiality of the data. Each patient received the appropriate care in accordance. All efforts were made to protect the patient's privacy and dignity, and none of the patients' data was shared with anybody outside the medical research community. Patients whose follow-up was not adhered to were removed from the research.

Authors contribution

All authors are equally contributed.

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