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Analysis of the Short Term Change in Subfoveal Choroidal Thickness in Eyes With Age Related Macular Degeneration Using Optical Coherence Tomography

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Abstract

Background and Objective—To measure the subfoveal choroidal thickness in patients with age-related macular degeneration (AMD) over 6 months.

Study Design/Patients and Methods—A retrospective, observational study of patients with AMD followed for 6 months at the New England Eye Center. Baseline and 6 month subfoveal choroidal thickness was measured using spectral domain OCT and compared.

Results—For the entire cohort there was statistically significant thinning of the subfoveal choroidal thickness at 6 months compared to baseline, which was driven by the cohort of patients with neovascular AMD [181.2 $\pm$ 75 μ m to 173.4 $\pm$ 63 μ m] $p=0.049$. (Figure and Table 1).

Conclusions—There was a statistically significant decrease in subfoveal choroidal thickness observed in this cohort of patients with AMD over 6 months, but it was driven by one subgroup, those patients with neovascular age related macular degeneration.

Introduction

OCT provides cross-sectional, three-dimensional, high resolution views of the retina *in vivo* in a non-invasive, reproducible manner.¹ Spectral domain (SD) OCT permits fast scanning speeds of up to 52,000 A-scans/second, and with improvements in SD OCT technology such as image averaging, and enhanced depth imaging (EDI), imaging through the choroid is now possible.^{2–6} The choroidal thickness has been evaluated using SD OCT in both normal and

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diseased states such as in patients with high myopia, age related macular degeneration (AMD), central serous chorioretinopathy (CSCR), and age-related choroidal atrophy.⁷⁻¹⁰

AMD is the leading cause of irreversible visual impairment among the elderly worldwide.¹¹⁻¹² OCT generated macular thickness maps have proven useful in monitoring the progression and response to treatment in neovascular AMD (nAMD) after anti-vascular endothelial growth factor (VEGF) treatment, and more recently, SD OCT and enhanced depth imaging (EDI) are being used to examine the choroid of patients with AMD.^{10,13,14} Choroidal thinning has been described in patients with AMD compared to age-matched controls, however there has not been significant investigation regarding the change in the subfoveal choroid thickness of AMD patients over time.^{10, 15, 16} The purpose of this study is to examine the change in subfoveal choroidal thickness in patients with neovascular AMD (nAMD) and dry AMD over a 6 month time period using SD OCT.

Study Design/Patients and Methods

This is a retrospective observational study investigating the change in subfoveal choroidal thickness in patients with both neovascular and dry AMD over a time period of 6 months. This study was approved by the Institutional Review Board of Tufts Medical Center, and was conducted in adherence to the tenets of the Declaration of Helsinki. Patients previously diagnosed with AMD who were followed for 6 months at the New England Eye Center, Tufts Medical Center, between 11/2009-11/2010 were included in this study. All patients included in this study underwent a comprehensive ophthalmologic examination with fundus biomicroscopy, color fundus photography, best corrected Snellen visual acuity, and OCT imaging. OCT imaging was performed using Cirrus-HD OCT software version 4.5. The software version allows for the acquisition of high-definition 1-line raster scans that are constructed from 20 B-scans obtained at the same location and processed using a unique Selective Pixel Profiling system (Cirrus HD-OCT; Carl Zeiss Meditec.). The 1-line raster scan, which is a 6 mm line scan consisting of 4096 A-scans, has an axial resolution of 5-6 μm and a transverse resolution of 15-20 μm . Images were taken with the vitreoretinal interface adjacent to the zero-delay, and were not inverted to bring the choroid adjacent to zero-delay, as image inversion using the Cirrus software results in a low-quality image. These high definition images provide increased definition of retinal layers, as well as more posterior structures, such as the choroid-sclera junction. All reviewed scans had an intensity of 6/10 or greater, were taken as close to the fovea as possible, with adequate visualization of the choroid-sclera boundary.

The subfoveal choroidal thickness was measured manually using the Cirrus linear measurement tool (version 4.5, Carl Zeiss Meditec, Dublin, CA). The measurements were taken from the base of the hyperreflective retinal pigment epithelium to the hyporeflexive line corresponding to the sclera-choroidal interface junction. The same scan was used for all patients and the readers were masked from each other's results. Two measurements were taken at baseline and at 6 months by three independent observers, (J.F., V.M., L.B) and the average data were compared for each patient. Chart review was performed to collect information regarding duration of disease, number of intravitreal anti-VEGF injections,

visual acuity (VA), and concomitant retinal pathology. Highly myopic patients (> 6 D) were excluded secondary to known choroidal thinning.⁸

The results were also compared with age-matched controls, using data from a previous study by this same group. All statistics were calculated using SPSS software version 17.0 for Windows (SPSS, Inc, Chicago, Illinois, USA). The paired t-test was used to correlate mean subfoveal choroidal thickness values at baseline and at 6 months. Data are expressed as means $\pm$ standard error of the mean (SEM). P values ≤ 0.05 were considered to be significant.

Results

Of the initial 65 eyes of 52 patients identified, 16 eyes were excluded secondary to lack of follow-up, incomplete choroidal penetration on subsequent OCT scans, or follow-up scans with inadequate signal strength. There was one patient excluded because the outer boundary of the choroid was not visualized. This patient had a history of neovascular AMD and was noted to have a scar with fibrosis along with subretinal hemorrhage and intraretinal fluid on initial enrollment. On subsequent exam, the choroidal scleral boundary was not visualized secondary to poor penetration through the scar. Patients were sub classified as having dry AMD if there was no evidence of neovascularization such as intraretinal or subretinal fluid at any visit time point. This group included patients with geographic atrophy, drusen, and drusenoid or serous pigment epithelial detachments not associated with choroidal neovascularization. The dry AMD patients were not further categorized to assess for severity of disease. Patients were subclassified as having neovascular age related macular degeneration (nAMD), if there was evidence of neovascularization such as intraretinal or subretinal fluid at any visit time point. All patients classified with nAMD had subfoveal neovascularization. Patients were treated by different attending physicians with a combination of treat and extend and as-needed regimens with anti-VEGF therapy. In total there were 49 eyes from 39 total patients that had adequate 6 month follow-up, of these 30 eyes (61%) had nAMD, and 19 eyes (39%) had dry AMD. 22 were women (56%) and 17 men (44%), with an average age of 78.5 years (range, 59 to 93 years).

3 patients had one eye included in the dry AMD group and 1 eye included in the nAMD group. Of the patients with nAMD, no patients were treatment naïve: 23 eyes had received intravitreal ranibizumab, 12 eyes intravitreal bevacizumab, 2 eyes intravitreal pegaptanib, 1 eye intravitreal triamcinolone, and 5 eyes either photodynamic therapy or laser. Of patients that received PDT: 2 eyes had one session, 3 eyes 3 sessions, and 1 eye 4 sessions. None of these sessions were during or shortly before the 6-month period examined in this investigation. Three of the PDT treated eyes had thinner than average choroidal thickness.

Of the 30 eyes with nAMD, 14 eyes had received between 1-5 injections, 5 eyes between 5-10 injections, and 10 eyes between 11-20 injections prior to enrollment in the study. 10 eyes received a combination of treatments listed above prior to enrollment in the study.

For the entire cohort of AMD patients, there was a statistically significant thinning of the subfoveal choroidal thickness at six months compared to baseline [$181.2 \pm 75 \mu\text{m}$ to 173.4

+/- 63 μ m] $p=0.049$. (Figure and Table 1). This finding was driven by the subgroup of nAMD patients. In the subgroup of dry AMD eyes, subfoveal choroidal thickness did not demonstrate statistically significant change between baseline and 6 months [192.2 +/- 70 μ m to 190.8 +/-60 μ m] $p=0.824$ (Table 1 and Figures 1 and 2). In the subgroup of nAMD eyes, there was a statistically significant difference between subfoveal choroidal thickness at baseline and at 6 month follow-up [182.8 +/- 77 μ m to 169.1 +/- 62 μ m] $p = 0.015$ (Table 1, Figures 1 and 3).

In the nAMD group, which consisted of 30 total eyes from 27 total patients, 10 eyes (33%) demonstrated increased subfoveal choroidal thickness and 20 eyes (66%) demonstrated a decrease in subfoveal choroidal thickness at 6 month follow-up. The opposite pattern was observed in the subgroup of dry AMD patients, which consisted of a total of 19 eyes from 14 patients. 12 eyes (63%) demonstrated an increase in subfoveal choroidal thickness, and seven eyes (37%) demonstrated a decrease in subfoveal choroidal thickness at 6 month follow-up. This is demonstrated pictorially in Figure 4.

Discussion

When the above data was analyzed including both the dry and nAMD patients there was a statistically significant decrease in the subfoveal choroidal thickness over 6 months compared to baseline ($p=0.049$). On subgroup analysis however, it was clear that the nAMD patients, who made up the 61% of the cohort, drove this finding. The dry AMD patients did not demonstrate a statistically significant decrease over 6 months when examined as a subgroup. Although in both dry and nAMD groups there were some eyes that demonstrated an increase in choroidal thickness over 6 months, there was overall a statistically significant trend towards decreased choroidal thickness in the group considered as a whole. The increase in subfoveal thickness, which was observed in both subgroups, may represent an error intrinsic to manual measurements, or a natural variation in choroidal thickness. The choroid is a highly vascular structure whose thickness varies with intraocular pressure, perfusion pressure, nitric oxide production, and vasoactive substances such as circulating catecholamines, and is believed to be highly sensitive to small vessel disease, therefore it may be expected that there is some natural fluctuations of subfoveal choroidal thickness over time.²⁰⁻²³ There is also known diurnal variation in choroidal thickness with the choroid being thickest at night and thinnest during the day. A recent study by Chakraborty et al demonstrated an average choroidal thickness of 0.256 +/- 0.049 mm with a diurnal fluctuation of 0.029 +/- 0.016 mm. Patients included in this study had OCT imaging performed at various times throughout the day and therefore there may be some choroidal thickness variation due to differences when the measurements were taken.²⁴ In normal eyes on the Cirrus OCT, Manjunath et al. reported a subfoveal choroidal thickness of 272 $\pm$ 81 μ m with a sample size of 34 subjects, and a mean age of 51.1 years (range, 22 to 78 years), as well as demonstrating the reproducibility of choroidal thickness measurements by the same technique described in this study, with strong inter-observer correlation $r = 0.92$, $P < .0001$.¹⁷ Previous studies have demonstrated a 1.56 μ m decline in choroidal thickness per year of life, and therefore based on the normative data obtained on the Cirrus HD-OCT by Manjunath et al, the average choroidal thickness expected in normal patients with an

average age of 78.5 years would be 229 μm , which is significantly thicker than what was observed in both the dry and nAMD cohorts in our study.^{17, 25}

More recent work by the same group demonstrated a mean subfoveal choroidal thickness of 194.6 μm (SD 88.4; n=40) in patients with nAMD vs. 213.4 μm (SD 92.2; n=17) in patients with dry AMD, with a mean age of 78.6 years.¹⁰ Our data demonstrates similar baseline subfoveal choroidal thickness for patients with nAMD 182.8 $\pm$ 77 μm and dry AMD group 192.2 $\pm$ 70 μm , confirming that both the dry and nAMD patients have thinner than average choroids compared to age-matched normal.

There are two hypotheses to explain the choroidal thinning observed in this investigation. Patients with nAMD may have accelerated choroidal thinning due to vascular or metabolic factors, which may contribute to the pathogenesis of AMD. Another possibility is that treatment for nAMD, intravitreal anti-VEGF agents, may cause choroidal thinning.

VEGF is expressed in the retinal pigment epithelium of normal eyes where it is thought to be a trophic factor for the choriocapillaris and play a role in choriocapillaris survival and permeability. VEGF-A is a glycoprotein that is thought to have an important role in the regulation of the choroidal vasculature.^{18, 26, 27}

Therefore continuous VEGF blockage used in the treatment of nAMD through the use of anti-VEGF agents, may negatively affect the maintenance of the choroid. Clinically it has been demonstrated that retinal pigment epithelial cells undergo progressive atrophy in patients in nAMD patients undergoing treatment with intravitreal anti-VEGF therapy, although it is unclear if this is related to anti-VEGF treatment or the natural history of the disease.^{28,29}

Rahman et al found no correlation between subfoveal choroidal thickness and treatment with anti-VEGF agents, in a small case of 15 patients who were treated with 3 months of intravitreal anti-VEGF medication and compared to 15 treatment naïve nAMD patients. Of note, however this was a very small sample size, and choroidal thickness was not analyzed over time.³⁰ Conflicting data from Forte et al examined 34 patients with macular edema injected with intravitreal bevacizumab. Retinal and choroidal thickness was measured before and after one year of treatment, and in 24% of these patients, there was statistically significant choroidal thinning at one-year follow-up, suggesting that VEGF blockade may play a role in choroidal thinning.¹⁹

There are several limitations to this study. This examination did not sub-classify dry AMD patients using AREDS criteria to assess disease severity, as the sample size was small and the study was not powered to detect a difference in the sub cohorts of patients. It may be that patients with more advanced dry AMD have a rate of decrease in subfoveal choroidal thickness comparable to the nAMD group. Increased number of subjects with dry AMD would be necessary to investigate this. Dry AMD also has a different clinical time course than nAMD, so it may be that choroidal thinning does occur, but at a slower rate that would not be significant over a 6 month study. Future studies employing long term follow up would help elucidate choroidal thickness changes during the natural history of this disease process.

Another limitation is that with the Cirrus OCT, there is no way to be sure that the same retinal location is scanned at differing time points. This issue may be exacerbated in patients with poor fixation due to low vision. It is also difficult to determine the central foveal scan in the setting of retinal edema or choroidal neovascularization. This may contribute to choroidal thickness fluctuation that is unrelated to underlying disease process. In addition, measurements were manually performed; automated software would be a more objective evaluation of choroidal thickness.

In conclusion, this study suggests that there is a decrease in subfoveal choroidal thickness in subjects with nAMD over 6 months that was not observed in those with dry AMD over the same time period. It is unclear if this decrease represents the natural history of nAMD, or if it is related to treatment with anti-VEGF agents. Continued advances in OCT technology, such as choroidal segmentation, will allow for more accurate measurements of the choroid in the future and hopefully aid in further understanding of the role of the choroid in disease processes such as age-related macular degeneration.

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Figure 1.

A-D: Graphical representation of the subfoveal choroidal thickness in subjects with age-related macular degeneration (AMD) over six months with comparison to age matched controls. Total of 49 eyes with AMD from 39 patients. 30 eyes (61%) had neovascular AMD and 19 eyes (39%) had dry AMD at the start of the study.

Figure 2.

A-D: Choroidal thickness in a patient with dry AMD. [A,C] High definition Cirrus 1 line raster scans and [B,D] color fundus photographs from a patient with a history of dry AMD over 6 months.

Figure 3. Choroidal thickness in a patient with neovascular AMD. [A,C] High definition Cirrus 1-line raster scans and [B, D] color fundus photographs from a patient with a history of neovascular AMD over 6 months.

Figure 4. Scatterplot of the change in subfoveal choroidal thickness between baseline and 6 months in neovascular AMD (A) and dry AMD (B) subgroups.

Table 1

Subfoveal choroidal thickness in Age-related macular degeneration patients at baseline and at 6 months.

AMD Variant	Subfoveal Choroidal Thickness (um)		Total	P Value
	BASELINE	6 MONTHS		
Dry	192.2+/- 69.91	190.8 +/- 60.27	19 eyes	0.824
Neovascular	182.8+/- 76.71	169.1+/-61.98	30 eyes	0.015
All ARMD	181.2 +/- 74.82	173.4+/-62.73	49 eyes	0.049