OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY OF TIME COURSE OF CHOROIDAL NEOVASCULARIZATION IN RESPONSE TO ANTI-ANGIOGENIC TREATMENT

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Purpose: To use optical coherence tomography (OCT) angiography to monitor the short-term blood flow changes in choroidal neovascularization (CNV) in response to treatment.

Methods: In this retrospective report, a case of exudative CNV was followed closely with OCT angiography over three cycles of antiangiogenic treatment. Outer retinal flow index, CNV flow area and central macular retinal thickness were measured.

Results: Quantitative measurements of CNV flow area and flow index showed rapid shutdown of flow over the initial 2 weeks, followed by reappearance of CNV channel by the fourth week, preceding fluid reaccumulation at 6 weeks.

Conclusion: Frequent OCT angiography reveals a previously unknown pattern of rapid shutdown and reappearance of CNV channels within treatment cycles. OCT angiographic changes precede fluid reaccumulation and could be useful as leading indicators of CNV activity that could guide treatment timing. Further studies using OCT angiography in short intervals between antiangiogenic treatments are needed.

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Treatment of choroidal neovascularization (CNV) with monthly injections of antivascular endothelial growth factor (VEGF) agents is highly successful.[1] However, to reduce treatment burden, practice patterns tend towards individualized treatment based on disease activity using *pro re nata*[2] or treat-and-extend[3] regimens. The intervals between injections are guided by fluid reaccumulation on structural optical coherence tomography (OCT). This fluid reaccumulation may be detrimental to the long-term outcome.[4] Optical coherence tomography angiography is a novel technology that offers an alternative measurement of CNV activity that might be useful in guiding the customization of antivascular endothelial growth factor regimen. Here we report a demonstration of OCT angiographic measurement of the CNV response to treatment.

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Drs. D. Huang and B. Lumbroso had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: D. Huang, B. Lumbroso. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: D. Huang, Y. Jia. Administrative, technical, or material support: All authors. Study supervision: D. Huang, B. Lumbroso.

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Methods

This is a retrospective review of a case at Dr. B. Lumbroso clinic in Rome. Optical coherence tomography angiography (3 × 3 mm; 216 × 216 points; 3.8 seconds) was obtained using a 70 KHz, 840 nm wavelength commercial spectral OCT (RTVue-XR Avanti; Optovue, Inc, Fremont, CA) using the

split-spectrum amplitude decorrelation angiography algorithm[5] and three-dimensional orthogonal registration algorithm.[6] The scans were exported for processing by custom software at Casey Eye Institute under an IRB-approved protocol.

The OCT angiograms are primarily shown in *en face* views in which each pixel represent the maximum flow value detected within the relevant anatomy layers or "slabs."[7,8] We combine *en face* OCT angiograms from several slabs by the use of color coding (Figure 1A).

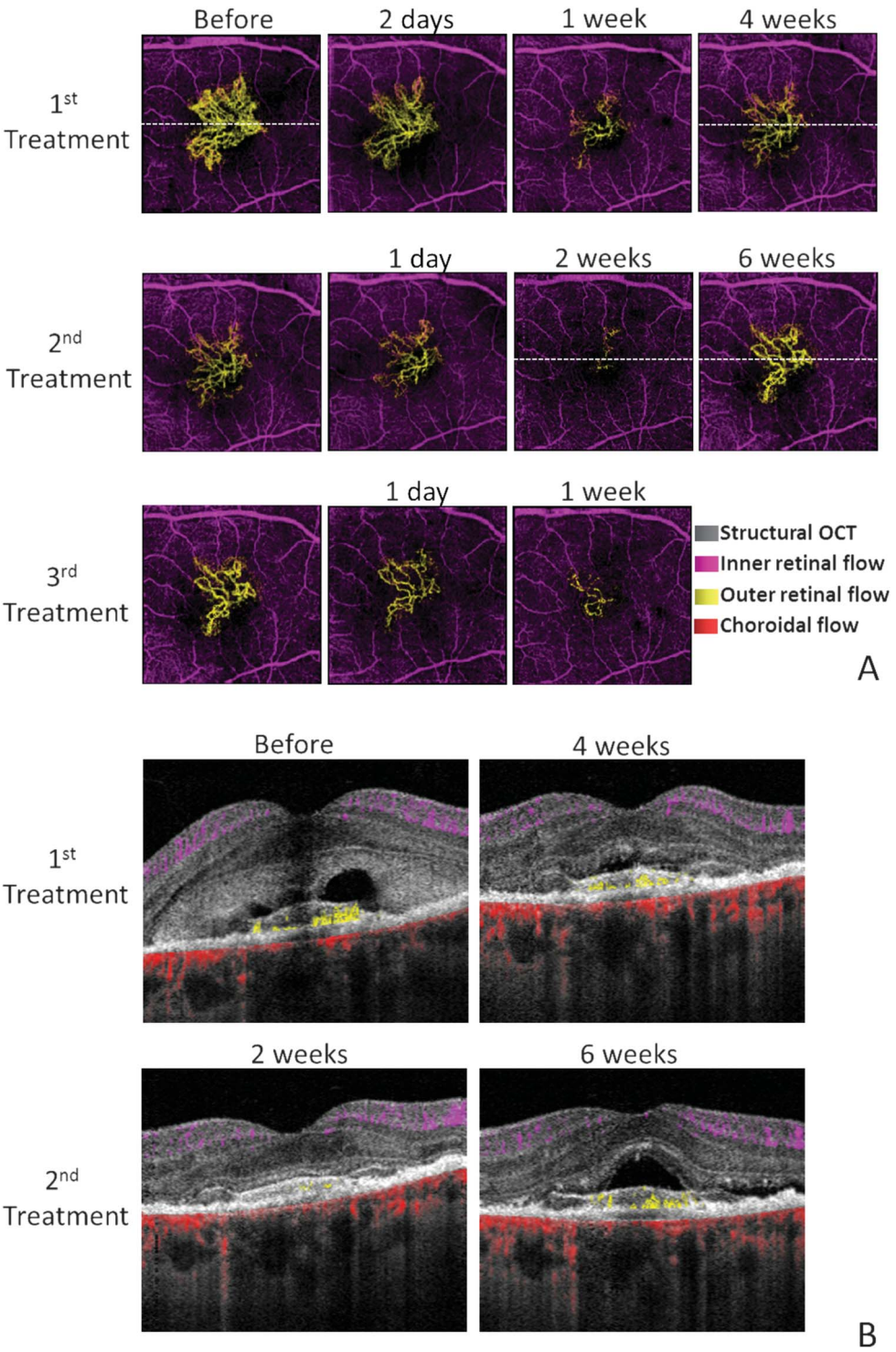

Fig. 1. Optical coherence tomography (OCT) angiography (3 × 3 mm) of CNV. **A.** *En face* OCT angiograms showing time course of CNV response to antiangiogenic treatment over three cycles. The dash lines indicate the locations of cross sections below. **B.** Cross-sectional OCT angiography showing subretinal fluid and CNV flow simultaneously at selected time points. CNV is above the retinal pigment epithelium (RPE) indicating type II CNV. By 4 weeks after the initial injection, subretinal fluid had largely been resorbed but flow in CNV was again active. Two weeks after the second injection, CNV flow had nearly ceased and the retina appeared completely dry. Six weeks after the second injection, there was a return of both CNV flow and subretinal fluid. The color code is as follows: inner retinal blood flow between the inner limiting membrane and outer plexiform layer-purple; outer retinal blood flow (CNV) between the outer plexiform layer and RPE-yellow; choroidal blood flow-red. Flow projection artifact in the retina pigment epithelium had been removed using a postprocessing algorithm.

The purple inner retinal slab shows flow from the internal limiting membrane to the outer boundary of the outer plexiform layer. The yellow outer retinal slab shows flow from the outer plexiform layer to the Bruch membrane. The red choroidal slab shows flow below Bruch membrane.

We also use composite cross-sectional OCT angiograms (Figure 1B) in which the flow signal is represented by the color scheme explained above, and the reflectance signal intensity (structural OCT) is shown in gray scale. The cross-sectional angiograms allow more precise visualization of the depth of CNV relative to retinal pigment epithelium (RPE).

The split-spectrum amplitude decorrelation angiography algorithm detects decorrelation (a normalized measure of variation) in OCT signal intensity over time, which could be produced directly by blood flow, or indirectly by flickering shadow cast by flow in the beam path. Thus, blood vessels in the inner retinal slab cast shadowgraphic flow projection artifacts on the deeper layers, interfering with CNV detection in the outer retinal slab. We use an automated computer algorithm to remove these flow projection artifacts and recover a clean CNV flow pattern on the outer retinal angiograms.[9] Briefly, projection artifacts were eliminated from the outer retinal angiograms by subtracting the inner retinal vascular patterns. A vascular pattern recognition algorithm then recovers the contiguous pattern of CNV network, and removes scattered residual artifacts. Choroidal neovascularization flow area was measured by the summation of pixel area with active CNV flow in the cleaned outer retinal angiogram. Outer retinal flow index was defined as the flow signal (decorrelation values)[5] averaged within the cleaned outer retinal angiogram. Central macular retinal thickness, measured from the internal limiting membrane to the RPE, was averaged in a 3-mm diameter circular zone centered on the fovea.

Results

A 73-year-old woman was initially referred 19 months before the current presentation, at which time fluorescein and indocyanine green angiography showed a medium-sized subfoveal classic CNV in the left eye, which had not been previously treated. She did not return for treatment until the current presentation, when she noted decreased vision in the left eye. The best-corrected visual acuity was 20/100. Slit lamp examination showed a small yellowish patch in the perifoveal region and retinal edema. Structural OCT revealed retinal elevation, subretinal fluid, and a hyper-reflective elongated area above retina pigment epithelium indicating Type II CNV.

Antiangiogenic treatment with intravitreal aflibercept injections were administered with a treat-and-extend regimen. Optical coherence tomography angiograms (Figure 1) showed noticeable reduction in CNV flow area by 1 days to 2 days post injection, with continued reduction at 1 week and 2 weeks. Choroidal neovascularization flow area and vessel density were reduced, probably due to the decreased flow or temporary closure of the smaller anastomoses. Significant reappearance of CNV was noticeable at 4 weeks after the first injection and again at 6 weeks after the second injection. The vascular pattern of the re-enlarged CNV (Figure 1A) was very similar to the initial pretreatment CNV, suggesting that the recurrence may be reopening of original channels rather than growth of new vessels. Comparing the CNV network before the third injection to the baseline, it is notable that there were fewer smaller channels, whereas the larger caliber channels remained. Quantitative measurements from OCT angiography (Figure 2A) showed reduction in CNV flow area and flow index over the first 2 weeks with subsequent return. Retinal thickness (Figure 2B) showed the fluid resorption over the first 4 weeks in the first treatment cycle continuing at least 2 weeks into the second treatment cycle, at which time no fluid remained (Figure 1B). But fluid reaccumulated under the retina 6 weeks after the second injection. Visual acuity (Figure 2B) continued to improve over the 3 treatment cycles.

Discussion

When we first studied CNV response to antiangiogenic treatment using infrequent OCT angiography scans coincident with treatment intervals, we found only small month-to-month reduction in CNV flow area and flow index that mirrored the slow resorption of fluid, as other investigators have also found.[10,11] This series showed that the apparent slow response was likely an artifact of infrequent imaging. When imaged more frequently, this case demonstrated dramatic shutdown of CNV flow in the initial 2 weeks after antiangiogenic injection, followed by reappearance of channels at 4 weeks and reaccumulation of fluids at 6 weeks. To our knowledge, this is the first known short-interval dynamic analysis of CNV treatment response using OCT angiography. Rebound of CNV flow area may be a leading indicator that precedes fluid reaccumulation and visual decline. The

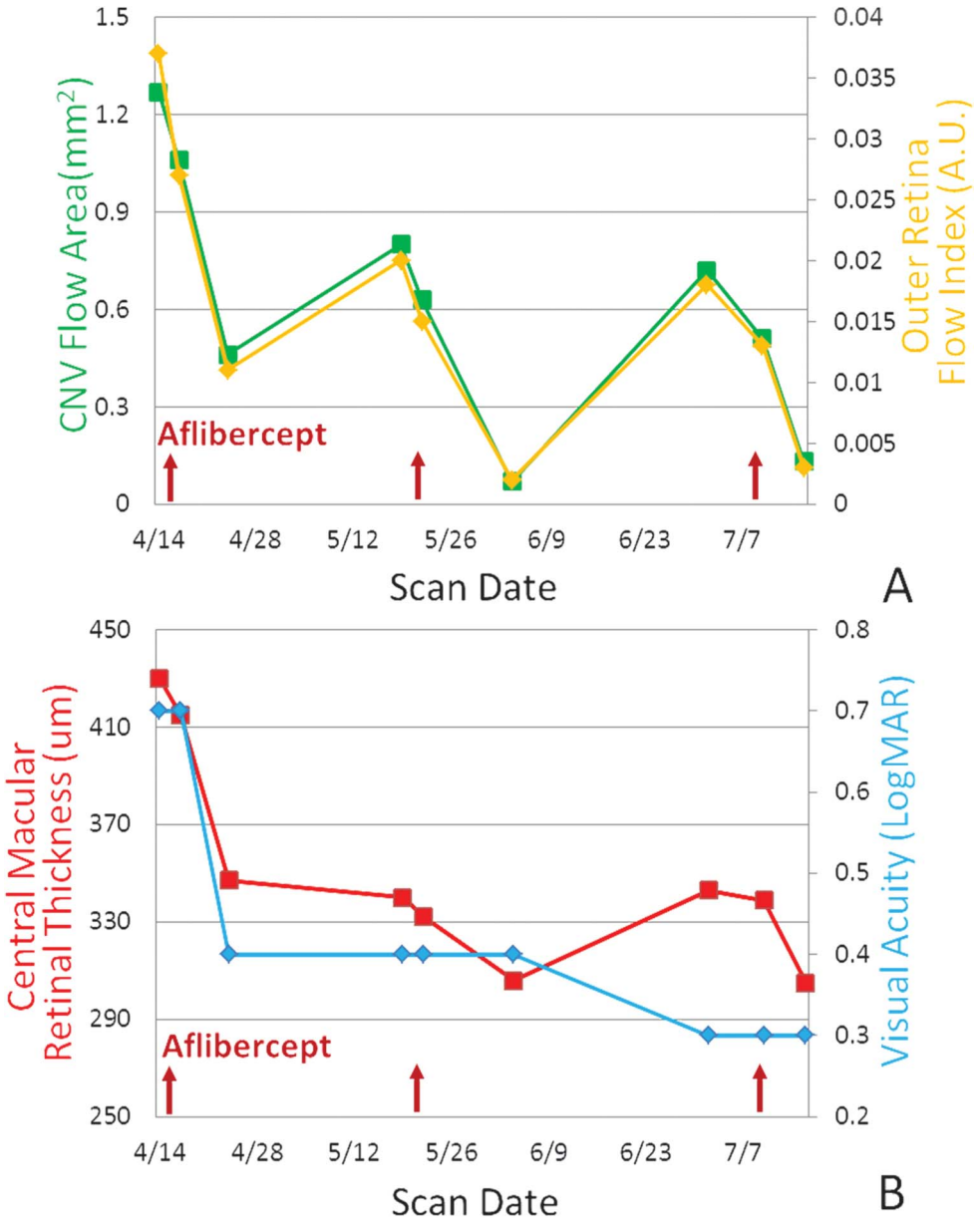

Fig. 2. Time course of CNV response to antiangiogenic treatment over three cycles. **A.** Quantitative OCT angiographic response. **B.** Structural OCT and visual acuity response. Red arrows indicate the injection dates in the year 2014.

time course in this case suggests that OCT angiography scans every 14 days to 15 days may be appropriate for determining the direction and rate of CNV flow area change and could provide information on whether extension of treatment interval would be successful. More study is needed to confirm this finding. If confirmed, then OCT angiography might be useful in guiding the proper selection of interval between injections so that fluid reaccumulation does not occur. It is also intriguing whether more frequent injections or continuous depot delivery of antiangiogenic medication that do not allow the reappearance of CNV channels might affect earlier and more permanent CNV regression.

Key words: optical coherence tomography angiography, imaging, neovascularization, retina, macula.

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