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under an HCQ regimen, the first retinal damage observed with SD-OCT concerns the inferior para foveolar area (Marmor 2012), which may explain why the decreased cone density we found was significant in the inferior but not superior quadrant.

The limitations of this study include the relatively small sample size and its cross-sectional design. As well, the camera's software systematically underestimates cone counts. Furthermore, the absence of cones on flood-illuminated AO images does not necessary imply their loss because the technique detects directionally backscattered light from normal intact photoreceptors but sometimes fails to detect remnant cones in a degenerating retina.

Our study agrees with the findings of Debellemanière and associates and suggests that retinal toxicity could start with decreased cone density in the inferior retina. Longitudinal studies are required to determine the predictive value of such findings for clinically screening HCQ maculopathy.

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Optical coherence tomography angiography in treated type 2 neovascularization undergoing monthly anti-VEGF treatment

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Editor,

The aim of this study was to characterize the longitudinal changes of treated type 2 choroidal neovascularization (CNV) (Freund et al. 2010) [showing neither intra- nor subretinal fluid on B-scan spectral-domain optical coherence tomography (SD-OCT)].

We used AngioVue OCT Angiography (OCTA; RTVue XR Avanti; Optovue, Inc., Freemont, CAm, USA) to image eyes undergoing monthly ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA and Novartis AG, Basel, Switzerland) injection for neovascular age-related macular degeneration (nAMD).

The local institutional review board approved this study. Fourteen consecutive treatment-naïve patients with nAMD, underwent monthly ranibizumab injections, were prospectively enrolled and after the loading phase, evaluated monthly with comprehensive ophthalmological examination and SD-OCT B-scan. As per protocol, patients continued to undergo monthly treatment even after the lesion was no longer active. Before the first injection, to establish the presence of new active CNV, we required evidence of leakage on fluorescein angiography (FA) and the association with presence of typical SD-OCT findings, including intra- or subretinal fluid. Choroidal neovascularization (CNV) was defined as type 2 if the lesion was above retinal pigment epithelium (RPE).

Optical coherence tomography angiography (OCTA) (3 × 3 mm and 6 × 6 mm macular cube) was performed starting 1 month after the loading phase and the plane of CNV identified (de Carlo et al. 2015). Also, the CNV area on OCTA *en face* images was manually delineated 1 month after the loading phase (first of 3 consecutive monthly visits showing no more active AMD after the loading phase) using ImageJ software version 1.48v (National Institutes of Health; available at http://imagejnihgov/ij/; Fig. 1A) (Kuehlewein et al. 2015). In addition, CNV size in the early phase on FA images was measured at the time of diagnosis (before the loading phase) (IMAGEnet; TRC-50× Topcon Instrument Corp, Tokyo, Japan). Measurements were taken by two different trained graders (MS, DDG). Two authors (LQ, FS), masked to the timing of the images, analysed qualitatively the OCTA images with respect to CNV appearance at baseline examination and its change over time, including shrinkage of vessels at the edge of the main neovascular complex, the decrease in the density of fine vessels and also the appearance of subretinal fluid on B-scans.

The CNV size during the follow-up (one-way analysis of variance with the Dunnett) and the relationship between changes in CNV size and different variables at baseline (linear regression analysis) were explored ($p < 0.05$).

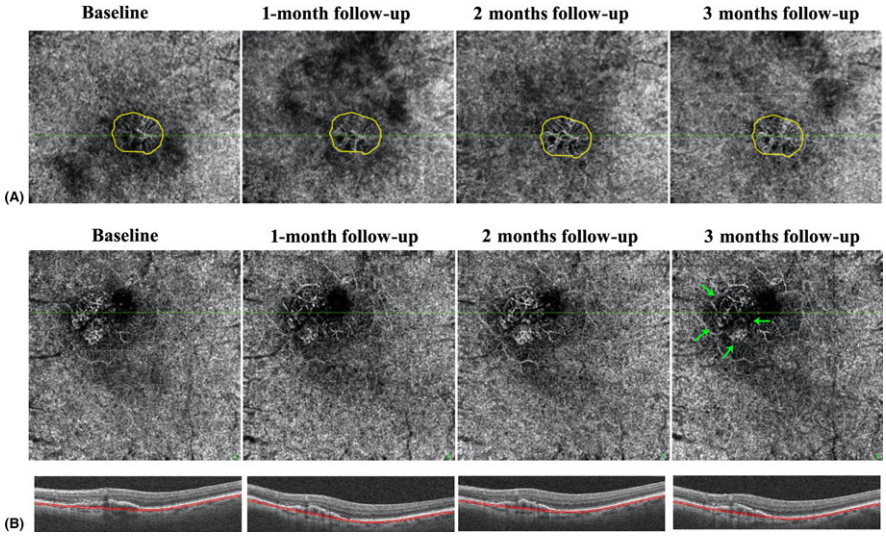

Fig. 1. Optical coherence tomography angiography (OCTA) C-scan (3 × 3) of case #04 (A) and case #06 (B – 30-μm thick) with type 2 choroidal neovascularization. (A) example of greatest area measurements (yellow lines) of the choroidal neovascularization (CNV) on sequential optical coherence tomography angiograms for subject #04. The CNV lesion does not show any significant changes over time. (B) *en face* optical coherence tomography (OCT) angiograms showing time–course of CNV after treatment with intravitreal anti-VEGF: the lesion size and the main vascular complex over do not show any significant changes over time. A reduction in the capillary network of fine vessels within the CNV is visible at the end of the follow-up (green arrows). The corresponding cross-sectional OCT B-scans with the segmentation lines (bottom) show the absence of subretinal fluid and a marked involution of the neovascular lesion after ranibizumab treatment.

Twelve eyes of 12 patients with treated type 2 CNV (mean age 75.6+/−9.4 years) for three consecutive monthly visits after the loading phase were investigated (two eyes excluded because of low-quality images). Mean duration of symptoms at time of diagnosis was 30.2+/− 27.1 days, and mean size of CNV at FA was 5.65+/−10.35 mm^2. Mean time from CNV diagnosis to the lesion being no more active was 3.9 months (average of 3.9 intravitreal injections).

Quantitative OCTA analysis revealed a CNV area of 4.99+/−3.99 mm^2 at baseline examination, which did not change significantly (5.15+/−4.27 mm^2; p = 0.99) after 3 monthly ranibizumab injections (Fig. 1A).

Qualitative OCTA analysis revealed the persistence of the main neovascular complex in 9/10 eyes (Fig. 1B). However, a subtle shrinkage of vessels at the edge of the lesion and reduction in the capillary network of fine vessels within the neovascular lesion was observed in all eyes (Fig. 1B).

No significant relationships were found between age, gender, duration of symptoms, CNV area on FA at time of diagnosis and change in CNV size on OCTA during follow-up (p > 0.05).

Our quantitative and qualitative analysis of treated type 2 CNV undergoing monthly anti-VEGF treatment reveals that while the size of the lesion as well as the main neovascular complex does not change during the short-term follow-up, the capillary plexus shows attenuation. These results suggest that anti-VEGF therapy might not be effective in reducing the main neovascular complex size possibly because of the presence of pericytes overlying the endothelial cells, even in the monthly regimen (Benjamin et al. 1998).

The main limitation could be related to the inability to be sure that the image quality of the OCTA signal in the area analysed was the same in all visits.

Our findings, in line with previous publications (Jia et al. 2014; de Carlo et al. 2015; Kuehlewein et al. 2015), suggest that OCTA can be considered as a valuable tool for monitoring treated CNV.

In conclusion, using *en face* measurements of OCTA images, we showed that further reduction in size is not seen once the type 2 CNV lesion becomes no more active.

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Switching to aflibercept in patients with neovascular age-related macular degeneration not responding to bevacizumab: a pilot study

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Editor,

Anti-vascular endothelial growth factor (VEGF) therapy has become the mainstay of neovascular