Comparison of SD-Optical Coherence Tomography Angiography and Indocyanine Green Angiography in Type 1 and 2 Neovascular Age-related Macular Degeneration

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Submitted: August 31, 2017
Accepted: March 27, 2018

PURPOSE. The purpose of this study is to compare the ability of spectral domain optical coherence tomography angiography (SD-OCTA) and indocyanine green angiography (ICGA) to detect and measure lesion area in patients with type 1 and 2 choroidal neovascularization (CNV).

METHODS. Types 1 and 2 neovascular AMD (nAMD) were included in this prospective and observational case series. ETDRS best-corrected visual acuity (BCVA), ophthalmic examination with funduscopy, OCTA (AngioVue), fluorescein angiography (FA), ICGA, and OCT (Spectralis) were performed. CNV measurements were done manually by two experienced graders using the systems’ innate region selection tools.

RESULTS. Forty eyes of 39 consecutive patients with nAMD were included. Mean age was 77 ± 6.4 years, ETDRS BCVA was 67 ± 13 letters, and 11 eyes were treatment naive. Nineteen CNV lesions were classified as type 1 and 21 as type 2. ICGA was able to identify CNV in all eyes. By contrast, OCTA detected CNV in 95% of type 1 and 86% of type 2 nAMD eyes. Mean overall CNV area (CNV-A) was 2.8 ± 2.7 mm² in ICGA and 2.1 ± 2.7 mm² in OCTA. Both lesion types CNV-A appeared significantly smaller in OCTA compared with ICGA (P < 0.01). Bland-Altman plot revealed a mean difference (bias) between OCTA and ICGA CNV-A of 0.76 ± 1.74 mm². Intraclass correlation coefficient (ICC) for CNV-A was 0.91 and 0.93 for ICGA and OCTA, respectively. ICGA CNV-A in the four OCTA-negative eyes (median 4.7 mm²) was not significantly different from the 36 OCTA-positive eyes (median 1.7 mm²).

CONCLUSIONS. Type 1 and 2 CNV-A were significantly smaller in OCTA than in ICGA. OCTA was generally less successful in detecting CNV than ICGA in patients who were included into this study based on FA and OCT. However, OCTA detected all type 1 lesions except for one, indicating that the SD-OCTA signal is limited by detection limits of blood flow velocity rather than lesion type. Further efforts are needed pushing the limits of lowest detectable and fastest distinguishable flow until OCTA can deliver realistic qualitative and quantitative imaging of type 1 and 2 CNV for diagnosis and monitoring.

Keywords: OCT angiography, ICGA, type 1 AMD, type 2 AMD, neovascular age-related macular degeneration

Optical coherence tomography (OCT)1,2 and anti-VEGF therapy3-5 have revolutionized the diagnostic and therapeutic management of neovascular AMD (nAMD).

In pre-OCT times, nAMD was classified according to the location of the neovascular complex in relation to the RPE layer as classic overlying or occult underneath the RPE by using fluorescein angiography (FA)5 and occasionally indocyanine green angiography (ICGA), allowing improved light transmission through the RPE.6 As early as 1994, Gass et al.7 suggested that nAMD classification should be based on the structure and anatomical location of the CNV lesion, but this proposal was not adoptable until OCT became widely available. With increasing evidence from OCT-based visualization, CNV was recently recharacterized based on FA, OCT, and if necessary ICGA, and classified as type 1 neovascularization, which is located under the RPE, type 2, located above the RPE in the subretinal space but also originating from underneath the RPE, and type 3 intraretinal neovascularization, also known as retinal angiomatous proliferation (RAP).8,9 Another subtype of type 1 CNV was categorized as polypoidal choroidal vasculopathy (PCV).10

Current guidelines for the management of nAMD state that conventional intravascular fluorescein and/or ICGA are mandatory for diagnosis as they are the basis for visualization of the entire neovascular lesion.11-13 Follow-up may be effectively monitored by OCT alone.13 However, with new imaging technologies available such as OCT angiography, the question arises if spectral domain (SD)-OCTA could entirely replace invasive angiographic procedures. Although FA is the current standard for lesion typology and disease activity detection, including early features and late leakage, ICGA is used to visualize extension and morphologic pattern of a CNV lesion.
due to intraluminal restriction of the dye molecules and increased visibility of sub-RPE components with the longer wavelength used. Although the potential side effects of ICGA are described to be milder than those of fluorescein angiography, there are restrictions in its use because of allergy, and ICGA has never become established as a routine tool. Another burden of ICGA is the long examination time of 30 minutes, which requires more resources than OCTA. However, its increased visibility of sub-RPE CNV components allows comparison with OCTA slabs focusing on the sub-RPE area.

Today, OCT angiography (OCTA) is widely accepted as the first line diagnostic method and raises the hope that it could entirely replace the invasive and dye-based FA and ICGA. OCTA allows contact-free visualization of blood flow and thus retinal and choroidal vasculature. OCTA imaging uses decorrelation technology with high-frequency and dense volumetric scanning for the detection of flow-related changes between B-scans allowing dye-free generation of en face and cross-sectional images of retinal and choroidal circulation together with the OCT-based structural information. Despite the evident benefits of OCTA, it has not found its way into primary nAMD diagnosis, and treatment guidelines and FA/ICGA are still considered the gold standard for a comprehensive evaluation of lesion location and morphology.

Current efforts to fully explore and understand the capabilities of OCTA and to set the basis for future diagnostic and therapeutic criteria in nAMD include comparisons of FA and OCTA, as well as ICGA and OCTA with variable conclusions.

In this study, we examined ICGA and SD-OCTA images of patients with type 1 and type 2 nAMD and compared the findings regarding CNV area (CNV-A), as well as detection sensitivity for both entities.

### Methods

This prospective, observational, and consecutive case series was studied in adherence to the Declaration of Helsinki including current revisions and the Good Clinical Practice (GCP) guidelines. The study protocol was approved by the Ethics Committee of the Medical University of Vienna, and informed consent to participate was obtained from all patients. After assessment of Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA), patients underwent a complete ophthalmic examination including slit lamp, Goldman applanation tonometry, pupil dilation, and funduscopy. Patients eligible for study inclusion had to present with clear ocular media and active type 1 or 2 nAMD as assessed by FA and SD-OCT (SpectraLis OCT 2; Heidelberg Engineering, Heidelberg, Germany). ICGA evaluation was performed subsequently. Finally, OCTA volumes of the CNV lesion were captured using a commercially available SD-OCTA system (Software Version 2016.2.0.35; AngioVue; Optovue, Fremont, CA, USA).

Patients were grouped based on whether they had nAMD type 1 or 2, which was confirmed by two expert readers, and excluded if type 3, mixed lesions, or any eye disease was identified other than type 1 and type 2 nAMD. Noteworthy media opacities were also considered an exclusion criterion.

The OCTA system is based on SD technology and contains a laser with a wavelength of 840 nm and a speed of 70,000 A-scans/s with an axial resolution of approximately 5 μm. Retinal and choroidal vasculatures were imaged by using a repeated B-scan protocol recording two consecutive orthogonal B-scans at each position scanned (2 × 304 × 304 A-scans). Online motion correction coregisters the two orthogonal volumes, and a split-spectrum amplitude-decorrelation algorithm (SSADA) is applied for an improved signal-to-noise ratio. 3- × 3- and 6- × 6-mm OCTA scans were centered on the fovea to capture the full CNV lesion. Scan size was chosen to cover the whole CNV lesion. The automated layer segmentation displays a predefined vascular plexus, namely the superficial and deep plexus, the outer retina and the choroidal capillary layer in orthogonal view. The corresponding structural B-scans were used to guide placement of the two segmentation lines by moving the slab up and down to best visualize the CNV complex. The choriocapillaris segmentation slab was manually corrected if needed. This method allowed selecting images visualizing the largest extent of the CNV complex for quantitative analysis. Thereafter, the whole area containing abnormal vessel structures was manually delineated in the OCTA images, using the AngioVue systems’ innate area-measuring tool. Images had to cover the whole lesion area and were excluded if a bad signal-to-noise ratio or motion artifacts were present.

Optimal ICGA images used for delineation of CNV-A were taken within 1 to 10 minutes after dye injection. The area of the hypercyanescent lesion was manually selected using the Heidelberg region selection tool. As OCTA does not include leakage, we measured the core hypercyanescent areas, which were outlined in early ICGA images by identifying vascular networks at the site of the CNV complex but excluded areas of subsequent dye leakage.

### Statistical Analysis

Statistical analysis was performed using Prism 6 (SoftPad Software, Inc., La Jolla, CA, USA). All data are reported as mean ± SD, median, or as a percent of the total. Student’s t-test, Wilcoxon signed-rank test, and Bland-Altman method comparison were used to compare ICGA and OCTA measurements. SPSS (V.23; IBM Corp., Armonk, NY, USA) was used to calculate the intraclass correlation coefficient (ICC) between reader 1 and reader 2. A two-way mixed model with absolute agreement was used.
RESULTS

Patient Characteristics

Forty eyes of 39 consecutive patients (22 female, 17 male) with nAMD were included in this analysis. The mean patient age was 77 ± 6.4 years, ranging from 59 to 90 years. The mean ETDRS BCVA was 67 ± 13 letters, ranging from 31 to 90 letters; 11 patients were treatment naïve (Table 1).

CNV-A and Detection Sensitivity in ICGA and OCTA

In general, the CNV-A of all eyes with nAMD was significantly larger in ICGA (2.8 ± 2.7 mm²) than in OCTA (2.1 ± 2.7 mm², P < 0.01). This difference also remained significant when looking at eyes with type 1 and type 2 nAMD separately (Table 2). The mean type 1 CNV-A was 2.8 ± 3.0 mm² in ICGA compared with 2.4 ± 3.1 mm² in OCTA (P < 0.01). The type 2 CNV-A was 2.9 ± 2.5 mm² in ICGA and 1.9 ± 2.2 mm² in OCTA (P < 0.01). On average, OCTA CNV-A was 18.4% smaller than the same CNV-A assessed with ICGA.

ICGA detected type 1 and type 2 CNV in 100% of eyes with nAMD previously selected using FA and SD-OCT. By contrast, OCTA detected type 1 CNV in 95% and type 2 in 86% of eyes with nAMD (Table 2). Overall OCTA detection sensitivity was 90%.

OCTA failed to detect CNV lesions in four cases of nAMD. Three of these eyes had type 2 nAMD, with a median ICGA CNV-A of 3.8 mm², and one had a type 1 nAMD lesion (5.6 mm²). ICGA CNV-A in OCTA-negative eyes (median, 4.7 mm²) was morphologically not significantly different form OCTA-positive eyes (median, 1.7 mm²; P = 0.39; Mann-Whitney test; Fig. 1). However, excessive fluid was present in all of these eyes.

There was a strong correlation of CNV-A between OCTA and ICGA in type 1 (r = 0.874) and type 2 nAMD (r = 0.873; both P < 0.001; Figs. 2A, 2B). A Bland-Altman method comparison of all 40 eyes showed a bias of 0.76 ± 1.74 mm² and confirmed by ICGA that CNV-A was larger than in OCTA (Fig. 2C).

The ICC for OCTA readings was 0.91 and 0.93 for ICGA and OCTA readings, respectively, both showing excellent agreement.

DISCUSSION

OCTA is a noninvasive and consequently a non–dye-based technique, allowing visualization of retinal blood flow and therefore retinal architecture, initially and during the course of disease.21 Obviously, the method allows for a distinct visualization of vascular patterns, as leakage is most likely not obscuring the vascular features, which can be depicted in detail, resulting in a similar appearance as ICGA. Because ICGA is independent of blood flow characteristics, especially speed, it should be superior in detection sensitivity and offer a comprehensive representation of the neovascular net at any sub-RPE location. Therefore, we analyzed CNV presence and area using a triple approach with a primary typologic classification based on conventional FA and SD-OCT, subsequent quantitative evaluation by ICGA, and comparison to the lesion characteristics in OCTA imaging.

This concise approach proved that OCTA visualizes a statistically significantly smaller CNV-A than ICGA and that this is true for both type 1 and type 2 nAMD (see examples of nAMD type 1 and 2 in Figs. 3 and 4). This finding confirms previous studies in eyes with PCV and type 1 nAMD, where lesion sizes were statistically significantly smaller in OCTA than in ICGA without the systematic approach used in our study differentiating between lesion types.

Further, we found a strong correlation between OCTA and ICGA regarding CNV-A, indicating the absence of a pronounced variability in this study cohort, and a constant difference between the two methods. The median CNV-A difference between ICGA and OCTA was as high as 18.4%. However, it has to be considered that four patients were excluded from this correlation analysis as OCTA failed to delineate a distinct CNV lesion (Fig. 5) due to a high amount of fluid present. In addition, we compared all data using the Bland-Altman method comparison, which revealed a mean difference (bias) between OCTA and ICGA CNV-A of 0.76 ±
1.74 mm². Consequently, it can be clearly appreciated that CNV-A was substantially underestimated by OCTA.

Recent studies have shown that monthly anti-VEGF treatment leads to a decrease in CNV size and loss of small vessels, reaching a maximum regression at 12 to 18 days after treatment. However, at approximately 35 days, vessel proliferation restarts and preexisting larger vessels appear even thicker, which is thought to be due to vessel pruning. This learning has already been introduced in the preceding era of photodynamic therapy where the neovascular lesion “disappeared” by conventional FA standards, but was clearly found to persist by ICGA and refilled quickly during follow-up. Despite the intriguing option to visualize and measure lesion size by OCTA with all its presumed details, this strict ICGA comparison reveals the deficiency of OCTA-based quantitative CNV monitoring. Rather than SD-OCTA resolution of the lesion, a slowing of perfusion speeds most probably contributes to a smaller appearance. On the other hand, it cannot be excluded that ICGA overestimates the size of the CNV; this remains to be investigated.
Thus far, it is not entirely clear if single vessels of CNV lesions completely vanish with anti-VEGF treatment or just become undetectable by OCTA using the SSADA algorithm. The OCTA system’s interscan time may be a reason for undetectable flow and consequently vessels and CNV-A. Long interscan times, which are not achieved with the commercially available SD-OCTA system used in this study, would be needed to detect very slow blood flow. For example, ultrahigh speed swept-source (SS) OCTA systems with motion correction are needed to compensate for eye motion artifacts leading to decorrelation noise. Previous studies have reported statistically significantly larger CNV demarcation areas for different SS-OCTA than for commercially available SD-OCTA systems. Further, an evaluation algorithm (e.g., variable interscan time analysis) as described by Choi et al., allows the interscan time to be increased from ~1.5 to 3 ms, which decreases the limits for the lowest detectable and fastest distinguishable flow and consequently reveals microvascular structures previously not seen. However, these OCTA systems are not yet commercially available.

FIGURE 4. Type 2 neovascular AMD in SD-OCTA, OCT, and ICGA images. This is a 85-year-old treatment-naive male patient; BCVA was 53 ETDRS letters. (A) Early FA lesion detail. (B) Late FA lesion detail. (C) OCT line scan of the CNV lesion with subretinal fluid, intraretinal cystoid spaces, and subretinal hyperreflective material (SHRM); OCTA segmentation lines were included in this b-scan. (D) ICGA lesion detail at 30 seconds. (E) ICGA CNV lesion detail at 15 minutes. (F) OCTA automatically segmented choriocapillaris layer. (G) OCTA automatically segmented outer retina. (H) CNV lesion size in ICGA after 5 minutes measuring 2.08 mm² encircled in yellow using the Heidelberg Spectralis area measuring tool. (I) CNV lesion size in OCTA choriocapillaris layer measuring 1.34 mm² using the AngioVue area measuring tool.
available. Analyses of various SS-OCTA prototypes have already shown their superior ability regarding CNV detection compared with SD-OCTA. Certain areas of the CNV lesion may not be detectable in SD-OCTA because of very slow or fast blood flow. This is not the case in ICGA, as the dye will eventually stain the whole CNV lesion during the 30 minutes of examination, independent of blood flow velocity. This may be a reason why CNV-A is smaller in SD-OCTA than in ICGA. Another reason for CNV lesions appearing larger in ICGA is that ICG leaks discretely outside of choroidal vessels. ICGA images evaluated in this study were taken 1 to 10 minutes after dye injection when leakage occurs. However, care was taken not to count areas of dye leakage as CNV-A for this method comparison. Also, a methodologic bias could be the reason for the difference between ICGA and OCTA CNV-A. However, this error would most probably lead to a strict over- or underestimation in one image modality, which was not the case in this study. Further, we found the same results regarding CNV lesion area when excluding the five eyes scanned using a 6 × 6-mm scan pattern. A higher sampling density in a smaller volume (3 × 3 mm) could potentially increase CNV detection. Yet, previous studies showed the same results, namely larger CNV-A in FA and ICGA compared with OCTA.

This study confirms that OCTA is able to detect type 1 and type 2 nAMD in 95% and 86% of cases, respectively. Overall, OCTA detection sensitivity was 90%. Previous studies report a wide range of sensitivities between 32% and 87% for commercially available SD-OCTA systems without differentiation of lesion types. By contrast, ICGA was able to detect either type 1 or type 2 nAMD in 100% of patients, who were previously selected using FA and OCT. This proves the ability of SD-OCTA to overcome the RPE barrier which is in many respects a limitation of OCT-based imaging due to non-transmission of the RPE layer. The anatomy of the lesion type is obviously not problematic in CNV visualization as clearly proven in our analysis.

The small sample size of this study must be considered a limitation. Artifacts, which may make the interpretation challenging for nonexperienced readers, are another limitation of OCTA technology. Imperfect layer segmentation may also contribute to artifacts. Manual correction of retinal layer segmentation is required for accurate interpretation. Moreover, the field of view of OCTA and ICGA images was different, as well as the software used to measure the CNV lesion area, which could also be a reason for the supposed overestimation of CNV lesion size with ICGA compared with OCTA. This question could be attributed in future using devices allowing coregistration of OCTA and ICGA images.

This comparative study is of clinical relevance because an exact understanding of established imaging methods compared with new, evolving technologies is a prerequisite for the definition of future diagnostic and retreatment criteria. For a correct understanding of the pathophysiology of nAMD and the therapeutic response to antineovascular treatment, the option to quantitatively measure CNV area is obviously very promising. The next generations of SD- and SS-OCTA, which are now becoming available, may overcome the drawbacks of

FIGURE 5. This is a treatment-naive, 76-year-old male patient with an ETDRS VA of 53 letters. Images show an ICGA-positive but OCTA-negative feature, which is most probably due to the high amount of fluid present. OCTA: (A) Superficial retinal plexus. (B) Deep retinal plexus. (C) Outer retina. (D) Choriocapillaris layer with evidence of fluid (black area) and projection artifacts (vessel structures equal to superficial layer). FA: (E) Early phase of FA and (F) late phase of FA with hyperfluorescent foci and drusen staining. ICGA: (G) Early phase of ICGA and (H) late phase of ICGA, showing pronounced blockage of choroidal signal by the subretinal fluid and serous PED, as well as a hypercyanescent area adjacent to the serous PED. (I) OCT line scan of the CNV lesion with subretinal fluid and huge serous pigment epithelial detachment.
current SD-OCTA technology and eventually replace invasive and time-consuming FA and/or ICGA for eyes with type 1 and type 2 nAMD. A comparison of FA, ICGA, and OCTA is planned as a next step.

Summarizing, CNV-A was statistically significantly larger in ICGA than in OCTA in type 1 and type 2 nAMD. A good correlation between OCTA and ICGA CNV-A was found for both type 1 and type 2 nAMD (r = 0.874 and r = 0.873, respectively), but a Bland-Altman comparison showed a bias of 0.76 ± 1.74 mm². The median relative difference between ICGA and OCTA CNV-A was approximately 20%. In conclusion, SD-OCTA images are not yet better than or equivalent to ICGA in terms of CNV-A and detection sensitivity in type 1 and type 2 nAMD. An alternative for diagnosis and follow-up in eyes with OCTA-positive CNV lesions. Currently, a negative SD-OCTA scan with active edema should, however, lead to dye-based angiographic examinations.

Acknowledgments
Disclosure: R. Told, None; S. Sacu, None; A. Hecht, None; M. Baratisis, None; K. Eiblenberger, None; M.E. Kroh, None; S. Rezar-Dreindl, None; F.G. Schlani, None; G. Weigert, None; A. Pollreisz, None; U. Schmidt-Erfurth, None

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