Evaluation of the clinical utility of optical coherence tomography angiography in age-related macular degeneration

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ABSTRACT

Background/Aims To evaluate the ability of optical coherence tomography angiography (OCTA) to identify the presence or absence of choroidal neovascularisation (CNV) and CNV activity in age-related macular degeneration (AMD).

Methods Clinical parameters, fundus fluorescein angiography (FFA), indocyanine green angiography (ICG) and spectral-domain optical coherence tomography (SD-OCT) were used as the gold standard to determine disease activity. OCTA imaging was performed on the same day and was graded by two masked retina specialists for the presence or absence of CNV. Traditional multimodal imaging and OCTA findings were compared.

Results One hundred and fifty-two eyes of 106 patients with AMD were retrospectively reviewed. Of these, 59 eyes had wet AMD and 93 had dry AMD with high-risk drusen. OCTA had 85.4% and 79.3% specificity and sensitivity, respectively, in determining the presence or absence of CNV. OCTA was 69.5% accurate in determining active CNV. False positives and negatives were 21.6% and 8.0%, respectively.

Conclusions This study suggests that en-face OCTA images allow a moderate ability to identify CNV and that OCTA alone is weak at recognising active CNV requiring treatment in AMD.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of visual impairment in the population over 50 years in developed countries.1 2 There are two main forms of AMD: wet or neovascular AMD (nvAMD) and dry or non-neovascular AMD (non-nvAMD). The major cause of vision loss in nvAMD is due to the development of choroidal neovascularisation (CNV), which leads to photoreceptor damage secondary to exudation of blood, lipid or fluid exudation.3 4 CNV is difficult to identify by clinical examination alone. Developments in imaging have been helpful in better identifying CNV including fundus fluorescein angiography (FFA), indocyanine green angiography5 and assisted structural studies including spectral-domain optical coherence tomography (SD-OCT) which is also helpful in identifying the exudative consequences of fluid accumulation including retinal thickening and oedema.6

Although FFA is currently considered the gold standard imaging for CNV; it has several drawbacks including the risk of reaction to the fluorescein dye and the need for intravenous access. Optical coherence tomography angiography (OCTA) offers the advantages of vascular visualisation using a non-invasive, dye-less vascular visualisation and generates depth-resolved, three-dimensional images with a rapid acquisition. Reports have suggested that OCTA improves the diagnostic yield in nvAMD.7-9

Many studies have shown striking images of the presence of subretinal or subretinal pigment epithelium (SRPE) vessels in CNV. The sensitivity and specificity reported for CNV detection using OCTA in eyes with AMD vary widely from 50% to 86.5% sensitivity and 67.6% to 100% specificity, respectively.10-16 Thus, the clinical utility of OCTA images alone to assist decision making in the treatment of CNV is uncertain.

In this study, we aim to determine the clinical value of using en-face OCTA images in diagnosing the presence of CNV in AMD and to evaluate the activity of CNV and hence need for treatment in nvAMD. The presence of CNV and its activity was determined using SD-OCT, fluorescein angiography, clinical observations including vision change and patient history. Also, the OCTA en-face images were viewed in a masked manner to determine if new information could be gained from the vascular pattern, which would add to data already available from gold standard imaging modalities, to make clinical decisions.

METHODS

This retrospective case study was conducted according to the principles of the Declaration of Helsinki. Institutional Review Board (IRB) approval was acquired from the University of California San Diego for the review and analysis of patients’ data. Patient’s consent was obtained as per institutional protocol and all data and images were anonymised for patient’s safety. The study complied with the Health Insurance Portability and Accountability Act of 1996.

The patients included in the study were newly diagnosed nvAMD, current nvAMD patients undergoing treatment and contemporaneous non-nvAMD patients. All the patients had been diagnosed at a tertiary retina centre (Jacobs Retina
Center, Shiley Eye Institute, University of California San Diego, San Diego, La Jolla, California) by an experienced retinal specialist (WRF), between 2014 and 2017. A database search of the Jacobs Retina Center imaging reports was performed using the keywords ‘Age-related macular degeneration’ and ‘AMD’. The charts of all patients with AMD were gathered and reviewed. Inclusion criteria were (1) presence of intermediate AMD and worse, 2) a record of total follow-up for a minimum of 2 years without missed follow-up, (3) the use of a pro re nata (PRN) regimen of intravitreal anti-vascular growth endothelium factor (anti-VEGF) injections for the nv-AMD eyes and (4) the presence of OCTA on the database. Exclusion criteria were eyes with CNV secondary to a disease other than nvAMD. Additionally, eyes with ocular comorbidities including diabetic retinopathy, retinal vascular diseases, glaucomatous optic atrophy, corneal opacities and a history of previous vitrectomy were excluded. Finally, eyes with poor-quality images that were deemed ungradable were also excluded.

A complete ophthalmological examination including best-corrected visual acuity, slit-lamp biomicroscopy and indirect ophthalmoscopy following dilatation and retinal imaging including FFA, SD-OCT using the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) were performed in all eyes at baseline (first clinic visit) and at each follow-up visit. Clinical parameters along with retinal imaging were used as a gold standard to determine disease activity.

OCTA was performed on the same day as clinical examination, FFA and SD-OCT using the RTVue-XR Avanti SD-OCTA (Optovue, Fremont, California) with an axial resolution of 5 µm in tissue. The device acquires 70 000 A-scans per second, uses an 840 nm light source and a bandwidth of 45 nm to obtain split-spectrum amplitude-decorrelation angiography images and uses Optovue’s MCT software to correct motion from microsaccades.

Each OCTA scan covered a 3 mm×3 mm macular area for each eye. Automated segmentation was used and manual segmentation correction was performed as needed by an experienced retinal specialist (MC) to visualise the layer of interest. Two automated segmentation lines referencing the outer retina on the coregistered OCT B-scans were manually fine-tuned to be located at the outer aspect of the inner nuclear layer (inner boundary) and the level of Bruch’s membrane (outer boundary). The inner boundary was adjusted to include the innermost region with suspected CNV (characterised by interruptions in the RPE, the presence of a subretinal and/or SRPE haemorrhage, lipids, RPE detachment, subretinal fluid (SRF) or intraretinal fluid (IRF), or subretinal hyperreflective material). The outer boundary was adjusted to lie directly anterior to Bruch’s membrane, so that the minimal choroidal vasculature was included in the region imaged by OCTA.

‘Active’ CNV, needing treatment, was determined by signs of CNV with leakage on FFA within a 3×3 mm area centred on the fovea and the presence of IRF, SRF or SRPE fluid on SD-OCT. Both OCT and FA evidence of active CNV were required to be considered active CNV. Eyes without CNV consisted of patients with non-nvAMD, drusen and pigment changes without fluid, lipid, or haemorrhage on clinical examination and fundus photos as well as no fluid on SD-OCT. A PRN regimen of intravitreal anti-VEGF injections were given to patients with active CNV in this cohort as previously described by our group and others.

Disease activity was classified by two independent retinal specialists (MC, KCD) who reached consensus and had access to the charts and all the clinical and image information but were masked to the OCTA findings. The consensus was taken as the gold standard for CNV activity. Disease was classified as either active CNV which required treatment or inactive CNV which could be managed conservatively or non-nvAMD with no CNV but with drusen which could also be managed conservatively. These criteria have been published previously by our group. OCTA images were graded by two masked retina specialists (MJ, MJAP), who routinely use OCTA in clinical practice, based on the presence or absence of CNV on OCTA and masked to other images and clinical information. First, CNV was determined to be either present or absent based on standardised reference images consisting of en-face structural OCT of the superficial inner retinal plexus, deep inner retinal plexus, outer retina and choriocapillaris for each eye. Images showing an apparent neovascular plexus in the avascular space at choriocapillaris were considered to indicate CNV (online supplemental figure 1). If vessels were identified, then graders were asked to grade the vessels as finely branching (presumably active) or less branching, more mature (predominantly inactive). Also, they were asked to describe the shape of these vessels (lacy-wheel or sea-fan shaped), the presence of anastomosis and loops and then categorise them as active CNV or not based on the OCTA features (online supplemental figure 2). A senior retinal specialist (EN) was consulted in case of grading disagreement.

Each eye was classified in a binary manner regarding the presence of CNV on OCTA (yes or no) and the clinical standard imaging category (active CNV, needing treatment, yes or no). Using this data, a special kind of contingency table was generated. The table was evaluated using the Matthews correlation coefficient, the most informative metric to evaluate this kind of table. A coefficient of 0.5906 was calculated (range −1 and +1), this indicates that the findings were well correlated. Statistical analysis was performed using SPSS version 20.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Two hundred and nine eyes with AMD initially met the inclusion criteria for this retrospective study. Fifty-seven eyes were excluded following the exclusion criteria: 21 eyes were excluded due to poor quality of images, 13 eyes had previous vitrectomy and were excluded, 20 eyes were likewise excluded due to ocular comorbidities, including epiretinal membrane (12 eyes), glaucoma (6 eyes) and vascular occlusion (2 eyes). A further two eyes were excluded because of the absence of FFA, and one eye showed eccentric leakage or fluid on OCT B-scans outside of the 3×3 OCTA. Images from 152 eyes were used for the study. Fifty-one per cent were female and the mean age of the patients was 75.54 years (range, 42–97, SD ±9.79).

In the first part of the study, we studied the ability of the OCTA to determine the presence or absence of CNV in AMD patients. Of the 152 eyes, 39 had nvAMD while 93 eyes had non-nvAMD as assessed by FFA, SD-OCT and clinical studies. The non-nvAMD eyes had at least 24 months of follow-up and had no CNV identified by SD-OCT, clinical examination and colour photo at the baseline and for at least 6 months after baseline. Of the nvAMD eyes, 38 had active CNV by dye leakage on FA and fluid on SD-OCT, 21 eyes had inactive CNV, without leakage and without fluid on SD-OCT at the time of the OCTA.

Analysis of all AMD eyes

The specificity of OCTA for the detection of CNV was 85.37%, with a sensitivity of 79.28% and the positive and negative predictive values were 60.35% and 93.62%, respectively (table 1).
FALSE POSITIVES: Twenty-three of these eyes had a false positive for CNV on OCTA (15%). One eye was at the transition point between dry and nvAMD, there was no activity on SD-OCT or FFA but a small well-circumscribed CNV in the juxtafoveal area was identified by OCTA. This patient developed wet AMD 2 months after this scan (online supplemental figure 3). In two cases, false-positive CNV was associated with a region of flow evident into the area of choriocapillaris in a region of geographic atrophy (figure 1).

FALSE NEGATIVES: There were six false-negative OCTA cases (0.4%). In one of these cases, there was a large retinal pigment epithelial detachment, preventing visualisation of definitive vascular structures beneath the elevated RPE.

Analysis of nvAMD eyes
In order to simulate the clinic setting, in which decisions about treatment or retreatment are made from imaging we looked at eyes which are classified as nvAMD. We included eyes with ‘active’ CNV which included previously confirmed CNV in nvAMD and under anti-VEGF therapy for CNV and other eyes with well-treated inactive CNV which had been in remission for at least 6 months. We analysed subtypes of OCTA vascular anatomy to determine if vascular subtypes on OCTA could change our findings, this, however, had no predictive effect.

OCTA was 69.49% accurate in determining CNV activity and the need for treatment compared with the gold standard. False positives and negatives were 21.6% and 8%, respectively. The specificity of OCTA to detect the clinical activity of CNV was 87.5%, with a sensitivity of 31.58% and positive and negative predictive values of 72.92% and 54.54%, respectively (table 2).

FALSE POSITIVES: There were 13 eyes graded as false positive (22%). These eyes were classified as having active CNV, which was defined as visible CNV in the choriocapillaris segmentation on OCTA, but active leaking was not seen on FFA and IRF, SRF and SRPE fluid was not identified by SD-OCT (figure 2). These eyes were also previously treated with three or more intravitreal anti-VEGF injections. Additionally, these eyes were quiescent for at least 6 months after previous treatment with intravitreal anti-VEGF injections and remained without treatment for more than 6 months.

TRUE NEGATIVES: Our study included truly negative (inactive CNV) patients who had treatment cessation (using PRN treatment method) also termed, treatment holiday and who did not develop CNV activity for at least 6 months after imaging (10%). We looked at these patients to determine whether regressed or inactive vessels were seen by OCTA. This study included four eyes which had been in remission between 1.5 years and 2.4 years, 1 for 10 months and 1 for 5 years. In one of these patients, a dense pigmented scar could have masked the CNV as there was the masking of the choriocapillaris structures. In the remaining five patients, we found no explanation for

Table 1  Determination of presence or absence of CNV in eyes with active wet AMD and dry AMD

| Gold standard clinical parameters and retinal imaging | + | − | Total |
|------------------------------------------------------|---|---|------|
| Test outcome                                         | 35| 23| 58   |
| OCTA                                                 | 6 | 88| 94   |
| Total                                                | 41| 111|152 |

| Specificity | Sensitivity |
|-------------|-------------|
| 85.37%      | 79.28%      |

AMD, age-related macular degeneration; CNV, choroidal neovascularisation; OCTA, optical coherence tomography angiography.

Figure 1  Fundus imaging from a false-positive patient. (A) FFA and (B) SD-OCT showing, respectively, stained hyperfluorescence without leakage and discrete areas of RPE elevation without any fluid. Both corresponding to drusen and diagnosed as non-nvAMD, (C) OCTA at the level of the choriocapillaris demonstrated a plexus of choroidal vessels which might appear or be interpreted as CNV. Thus being a false-positive OCTA. CNV, choroidal neovascularisation; FFA, fundusfluorescein angiography; nvAMD, neovascular age-related macular degeneration; OCTA, optical coherence tomography angiography; RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography.

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inactive CNV membranes not identified on OCTA which were also not visible on FFA, suggesting that the abnormal vessels do disappear in some cases (figure 3).

DISCUSSION

AMD is a major health problem.3 Nv-AMD, in particular, places a heavy burden on healthcare systems globally requiring close monitoring and early treatment to avoid vision loss. This highlights the need for rapid, reliable tests to determine disease activity. This study aimed to investigate whether the use of OCTA alone is sufficiently sensitive and specific to identify disease activity in nvAMD to permit its use as an independent predictive test or whether it offers additional treatment information above current standard testing.

In our study, the specificity and sensitivity of OCTA for active CNV detection were moderately high at 85.4% and 79.3%, respectively. The results would mean that approximately 15% of eyes would have been falsely categorised as having active CNV if OCTA was used. The presence of subretinal vessels on OCTA does not always predict disease activity and we also found that eyes with non-exudative CNV may show subretinal vessels on OCTA. However, these lesions can remain quiescent for long periods of time, regress or wax and wane,15 26 the significance and evolution of such structures are not clear. In our study, we defined a false positive as a CNV which was identified as present on OCTA, but which showed no clinical activity using current gold standard techniques, that is without the presence of IRF, SRF, or SRPE fluid on SD-OCT and no angiographic activity or leakage for 6 months or longer in the absence of treatment.

Table 2  Determination of neovascular disease activity in eyes with wet AMD

| Gold standard clinical parameters and retinal imaging | Total |
|------------------------------------------------------|-------|
| Test outcome                                          |       |
| + 35                                                  | 48    |
| − 5                                                  | 11    |
| OCTA                                                 |       |
| + 5                                                   | 6     |
| Total                                                | 59    |
| Specificity                                          | 87.5% |
| Sensitivity                                          | 31.58%|

AMD, age-related macular degeneration; OCTA, optical coherence tomography angiography.

There are relatively few studies comparing current imaging techniques with OCTA in nvAMD. The sensitivity of CNV detection by OCTA ranges from 50% to 86.5% and the specificity of OCTA in detecting CNV has been reported to range from 67.6% to 100% in previous studies.10–16 The wide range of results for sensitivity and specificity is likely due to the small numbers of eyes examined in some of these studies. Additionally, the discrepancies may result from variations in exclusion/inclusion criteria and disease classification. Soomro and Talks,27 for example, used different disease aetologies in their determination of CNV activity mixing AMD, myopic CNV and central serous retinopathy. Their study showed that OCTA was able to detect CNV, but may have different results to our findings because of a differential case mix in the study sample.28

Figure 2  Fundus imaging from an elderly patient whose last anti-VEGF injection was 21 months previous to the imaging. (A) FFA and (B) SD-OCT B scans showing inactivity after treatment. (C) A 3×3 mm OCTA en-face with an evident CNV at the level of the choriocapillaris segmentation. For 7 months after this image, there was no leakage of CNV despite observation off therapy. Anti-VEGF, anti-vascular growth endothelium factor; CNV, choroidal neovascularisation; FFA, fundus fluorescein angiography; OCTA, optical coherence tomography angiography; SD-OCT, spectral-domain optical coherence tomography.

Figure 3  A case of true negative. (A) FFA showing no evidence of leakage. (B) SD-OCT shows subretinal drusenoid deposits (C) OCTA after 6 months without treatment shows no obvious CNV. CNV, choroidal neovascularisation; FFA, fundus fluorescein angiography; OCTA, optical coherence tomography angiography; SD-OCT, spectral-domain optical coherence tomography.
In the majority of previous studies, only the sensitivity and specificity of OCTA in determining CNV in AMD were tested. In the present study, our aim was to also determine the ability of OCTA to demonstrate actual disease activity. For this reason, in a sub-study, we used only patients classified clinically as either active nvAMD (patients being treated with PRN anti-VEGF therapy who received more than 3 injections and had ongoing visual symptoms, FFA leakage, and subretinal or intraretinal SD-OCT fluid), or inactive nvAMD (patients who had regressed CNV on a PRN protocol who remained treatment free with no evidence of FFA leakage or SD-OCT fluid for more than 6 months after our OCTA evaluation). We did this to test whether OCTA could identify features of clinical activity and hence help decide on whether the eyes needed treatment. Coscas et al had previously described the activity criteria of CNV on OCTA. Using these criteria, for nvAMD which had been treated, we found that the specificity of OCTA to determine active CNV in these eyes (neovascular disease activity in eyes with nvAMD), was 87.5%; however, the sensitivity was only 31.58% resulting in a large number of false-negative results. The specificity is similar to that of our larger AMD cohort but we note that the sensitivity to detect active CNV in eyes under treatment was disappointingly low.

To understand the false-positive results, we carefully examined 13 of our eyes that were quiescent after previous treatment with intravitreal anti-VEGF injections and were classified as falsely positive by OCTA. These eyes had no fluid leakage on FFA or intraretinal or subretinal fluid on SD-OCT despite observation off anti-VEGF for 6 months or longer. The false positives in all of these cases were due to clearly perfused vessels seen on OCTA, which did not leak on FFA images. The lack of fluid and leakage was confirmed on subsequent exams for 6 months or longer after the OCTA imaging with the patients remaining untreated. The fact that these patients are included in the PRN protocol also gives us the security of being sure that these patients were in remission, which would be difficult to assess with the treat and extend treatment paradigms.

Various groups have attempted to explain the presence of OCTA vessels in eyes with treated CNV. Fine capillary vessels of the neovascular complex in treatment naïve eyes are reported to significantly reduce in density after anti-VEGF therapy, while vessel density in a chronic setting following multiple injections becomes less responsive after each treatment. Gong et al suggest that the structure of the central subretinal neovascular trunk may differ from that of the surrounding fovea plexus and may be more resistant to anti-VEGF therapy because the endothelial cells are protected by overlying pericytes. They further suggest that smaller branching vessels consist of unprotected endothelial cells, which are more responsive to anti-VEGF therapy. However, we could not find a pattern suggesting active versus inactive CNV in our study including among our false-positive OCTA cases. Further study is needed to image eyes on standardised regimens to determine if the pattern of vessels on OCTA predict activity.

There are some limitations in this study. Only en-face images were provided for evaluation since this study wanted to compare the use of OCTA to the current gold standard. A future study comparing gold standard versus OCTA and SD-OCT would help determine whether OCTA could usefully add diagnostic information in combination with other imaging. Another limitation of this study was that the OCTA used in this study was not swept-source. Recent developments with swept-source may reveal different results with better resolution at depth and would also be worth investigating.

In summary, our study finds a relatively low sensitivity and specificity for en-face OCTA images alone in demonstrating the activity of CNV in nvAMD. As a result, OCTA may not provide consistent information to guide treatment when used alone, independent of other images, in the diagnosis and monitoring of nvAMD compared with the current gold standard. Studies are required to determine the best combination of studies to diagnose and monitor CNV in nvAMD.

Contributors MCC: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KD, MJ and MA-P: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; SB: Drafting the work or revising it critically for important intellectual content; D-UB: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EN: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. WN: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EN: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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