Hot debates in medical retina and imaging: Perspectives from the Controversies in Ophthalmology 2020 virtual conference

BY ROD MCNEIL

Controversies in medical retina and imaging were debated during the Controversies in Ophthalmology 2020 virtual conference held during two mid-day scientific sessions on 27 and 28 March 2020. The author recounts key perspectives and presents viewpoint recommendations from the Vision Academy, a global collaboration of expert ophthalmologists and retinal specialists.

Medical retina and imaging

OCT-A should be obtained routinely in cases of age-related macular degeneration

William Mieler, University of Illinois, USA, stressed the importance of supplementing dye-based fluorescein angiography (FA) and structural optical coherence tomography (OCT) with OCT-angiography (OCT-A) in the treatment of neovascular age-related macular degeneration (nAMD). Assessment and treatment of nAMD has evolved beyond the utilisation of FA (e.g. classifying occult and classic lesions), and even far beyond the use of structural OCT alone, with OCT-A becoming increasingly more beneficial and serving as an adjunctive tool. Structural OCT is a highly sensitive tool for detection and diagnosis of nAMD, e.g. fibrovascular pigment epithelial detachment (PED), subretinal hyperreflective material (SRHM) and various forms of retinal fluid. However, OCT-A may enhance the specificity of structural OCT, being helpful in cases where FA and / or OCT is difficult to interpret (e.g. SRHM) and its use may obviate the need for traditional FA in most cases. OCT-A has been noted to help confirm the presence of choroidal neovascularisation (CNV) in suspected cases without evidence of exudation [1]. Re-growth of CNV lesions on OCT-A may precede re-accumulation of fluid, and earlier treatment may save vision in the long term [2].

Structural OCT seems to remain the key imaging modality for guiding retreatment decision making in most patients with nAMD. Dense volume OCT scanning is helpful in the identification of intraretinal fluid (IRF), subretinal fluid (SRF) and sub-retinal pigment epithelium (RPE) fluid. The role of OCT-A in this setting needs to be further defined, yet certain features of the neovascularisation appear to be indicative of activity and need for retreatment. Dr Mieler recommended that OCT-A should be obtained in the majority of cases of nAMD, as it can aid in the classification, identification, treatment and retreatment of nAMD. OCT-A helps to better guide the therapy of active lesions and may lead to improved visual outcomes.

Peter Kertes, Sunnybrook Health Sciences Centre, Canada, observed that OCT-A is a relatively new imaging modality and there is still much to learn. Limitations can confound the interpretation of findings. Holmen et al. evaluated 406 OCT-A images from 234 eyes and reported a prevalence of severe artifacts of 53.5%, with shadow, defocus and movement seen as the most common artifacts [3]. Non-exudative or quiescent CNV is best detected with OCT-A while indocyanine green (ICG) angiography remains the best modality for polypoidal choroidal vasculopathy (PCV) currently. OCT-A images may have an important role to play next to OCT and FA/ ICG angiography, but treatment decisions should not be based on OCT-A in isolation, concluded Dr Kertes.

Ultra-widefield retinal photography is essential to managing diabetic retinopathy

Marc de Smet, MIOS, Switzerland, noted that standard 7-field imaging misses around one third of the retinal surface and diabetic retinopathy (DR) occurs outside Early Treatment Diabetic Retinopathy Study (ETDRS) fields in 40% of cases. Ultra-widefield (UWF) imaging compares favourably to mydriatic 7-field ETDRS-standards in grading DR [4], is superior to gold standard ETDRS imaging with respect to efficiency and ease and provides clinically useful additional data.

Predominantly peripheral lesions identified on UWF imaging are associated with increased risk of DR progression over four years [5]. The use of UWF FA allows the visualisation of significantly more diabetic retinal lesions and provides more accurate quantification of total retinal nonperfusion [6]. Nicholson et al. reported findings from a multicentre UK image study suggesting that eyes with nonproliferative DR to a threshold of 118.3 disc areas of retinal nonperfusion are at an increased risk of proliferative DR (PDR), and eyes with neovascularisation of the optic disc having the largest area of retinal nonperfusion [7]. Severity of diabetic macular oedema (DMO) appears to be positively correlated with retinal nonperfusion regions with leakage but negatively correlated with retinal nonperfusion regions without leakage, signalling the importance of vascular leakage in DMO [8].

Ultra-widefield angiography imaging demonstrates that nonperfusion is related to PDR and UWF OCT-A may also be of use for monitoring anti-vascular endothelial growth factor (VEGF) treatment response [9]. Reliable automated detection of referable DR using Optos UWF pseudocolour images has also been shown, achieving a high degree of sensitivity and moderate specificity [10].

Standard photography is sufficient for managing patients with DR, countered Michael Stewart, Mayo Clinic, USA. Management of DR should be considered according to disease classification: DMO can be followed by OCT, with optional photography and FA in most cases; DR severity is classified according to 7-field photography and UWF photography is

only starting to make an inroad; and finally, the management of PDR is best driven by clinical findings. While UWF photography visualises far beyond the 7-field photography, all pertinent findings can be identified with standard photography and fundoscopy. Ultra-widefield imaging is a helpful addition to retinal specialists' armamentarium and may have a role in certain cases, for example, managing patients with posterior uveitis or retinal vasculitis [11]. However, the best results in managing DR are obtained with OCT, careful clinical evaluation and standard ETDRS photography.

Neither OCT nor OCT-A is good enough for anti-VEGF follow-up all of the time – FA is needed at least 10% of the time

Susan B Bressler, Johns Hopkins University School of Medicine, USA, considered the role of OCT and FA in the management of CNV due to AMD. Anti-VEGF therapy for nAMD has revolutionised care with potential to preserve excellent visual acuity, based on frequent monitoring and prompt management of any disease activity. Today, following anti-VEGF therapy for nAMD, patients are typically examined at regular intervals with OCT, OCT-A and / or FA performed as indicated depending on the clinical findings and the judgement of the treating ophthalmologist.

Castillo et al. observed although OCT is highly sensitive, it has poor specificity, and recommended that OCT should not be used alone to detect CNV activity in patients being monitored [12]. Khurana evaluated agreement of OCT findings with presence or absence of fluorescein leakage from CNV [13]. Spectral-domain OCT was more likely than time-domain OCT to detect abnormalities when leakage from CNV was detected after anti-VEGF therapy. Referring to false-negatives on OCT, Dr Bressler said that she did not want to miss 10% that are active on the gold standard FA test (Table 1) [13].

The use of FA and OCT is determined in part by the treatment strategy used [14]; for instance, clinicians may choose to carry out FA and / or OCT examinations at baseline, perform monthly OCT for pro re nata (PRN, as needed) treatment and perform OCT examinations at each visit for treat-and-extend therapy. Fluorescein angiography may be added when there is a change in clinical status that is not explained by the OCT result [14]. Compared with FA, OCT-A does not provide leakage status and provides little added information that can be used to direct retreatment algorithms, noted Dr Bressler.

Dr Patricia Udaondo, Hospital Universitario y Politécnico La Fe Aiken, Spain, cautioned that FA does not provide three-dimensional anatomic information about retinal layers, the RPE or the choroid and provides no information about intraretinal, subretinal and subretinal pigment epithelium spaces. During follow-up, the primary issue that ophthalmologists are looking at is fluid and the intraretinal space is the location in which fluid affects vision the most, added Dr Udaondo. Optical coherence tomography is non-invasive and provides objective measurement of retinal thickening and extravasated fluid and has been validated against FA in the evaluation of retinal vascular leakage. Further, OCT detects abnormalities when fluorescein leakage from CNV is present and easily identifies signs of activity to treat (e.g. IRF or SRF / cystoid abnormalities).

Faridi et al. found that structural OCT alone has excellent sensitivity for CNV detection, while false positives from structural OCT can be mitigated with the addition of flow information with OCT-A (Table 2) [15]. Fluorescein angiography may play an important role in making a baseline assessment of newly diagnosed nAMD but its role in follow-up is limited as it is difficult to determine CNV activity compared with OCT. Combining OCT with fundus imaging and OCT-A can be sufficient for the follow-up of most patients without the need for invasive FA. If in doubt, it is better to treat nAMD rather than not treat, Dr Udaondo added.

Treatment of non-exudative CNV should begin when detected on OCT-A, even in the absence of OCT fluid or fluorescein leakage

Francesco Bandello, Vita-Salute University, Italy, explained that OCT-A allows the clinician to non-invasively identify treatment-naïve quiescent CNV, with a reported sensitivity and specificity of 82% and 100%, respectively [16]. These non-exudative lesions enlarge over time, study

Table 1: OCT detection of CNV activity and FA leakage findings.

59 eyes	**SD-OCT**	**TD-OCT**
Sensitivity	90%	59%
Specificity	47%	63%
	Interstitial fluid, cystoid abnormalities or subretinal fluid	
	On SD OCT	
FA leakage	No CNV activity	Yes CNV activity
No (n=29)	14 (47%)	16 (53%)
Yes (n=30)	3 (10%)	26 (90%)

Abbreviations: CNV, choroidal neovascularisation; FA, fluorescein angiography; SD-OCT, spectral-domain optical coherence tomography; TD-OCT, time-domain optical coherence tomography.
Adapted from: Khurana et al. [13].

Table 2: Sensitivity and specificity of OCT angiography to detect choroidal neovascularisation.

	Grader A	**Grader B**
Structural SD-OCT alone		
Sensitivity	100%	100%
Specificity	97.5%	85%
En face OCT-A alone		
Sensitivity	81.3%	83.3%
Specificity	92.5%	97.5%
En face OCT-A with cross-sectional OCT-A		
Sensitivity	100%	100%
Specificity	97.5%	100%

Abbreviations: OCT-A, optical coherence tomography angiography; SD-OCT, spectral-domain optical coherence tomography.
Adapted from: Faridi et al. [15].

data showing a rate of clinical activation of 6.6% during 12 months' follow-up, and can cause visual distortions, even in the absence of exudation [16,17]. A high rate of CNV growth and PED could predict the early activation of non-exudative CNVs and guide decisions to treat in absence of exudation [18]. Dr Bandello stressed that CNVs may be diagnosed without exudation and that different baseline OCT-A features may predict short-term activation (exudation).

Dr Udaondo commented that the reported rate of conversion of quiescent CNV to exudative AMD is variable depending on the published case series, with a maximum rate of 26-28%. Pfau evaluated the association between the presence of type 1 CNV and the localised progression of atrophy in AMD (98 eyes of 59 patients diagnosed with AMD) [19]. Results revealed a markedly reduced RPE atrophy progression in areas co-localising with quiescent and exudative type 1 CNV, an observation compatible with a potential protective effect of type 1 CNV on the RPE and overlying neurosensory retina. De Oliveira Dias et al. identified subclinical CNV in 14.4% (26) of 160 patients with intermediate AMD or geographic atrophy (GA) secondary to non-exudative AMD followed with OCT-A for 12 months [1]. Over 12 months, the cumulative incidence of exudation was 6.8% for all eyes with follow-up visits (n=134), 21.1% for eyes with subclinical macular neovascularisation (MNV) at time of first imaging and 3.6% for eyes without subclinical MNV. More frequent follow-up and home monitoring for eyes with subclinical MNV was recommended.

Serra et al. undertook a study to identify predictive activation biomarkers in treatment-naïve asymptomatic CNV in AMD (68 eyes with mean follow-up of 40 months) [18]. On structural OCT, quiescent CNV not converting to exudative AMD showed a preferential growth of the RPE detachment greatest linear diameter, while the exudative AMD group presented a preferential growth of the RPE detachment maximal height. The PRO-CON study found no significant benefit with aflibercept quarterly prophylaxis in preventing conversion to nAMD in high risk patients over 24 months. Dr Udaondo concluded that practitioners should not treat quiescent CNV lesions, as excellent monitoring tools are available, but should continue with close follow-up and watch for biomarkers of conversion to exudation.

Vision Academy in Retina 2020

Should anti-VEGF therapy be stopped in the event of an RPE tear?

Monica Lövestam-Adrian, Lund University, Sweden, explained that tears in the RPE are most commonly caused by PED in patients with exudative AMD and are recognised as a cause of severe central vision loss. She argued that treatment with anti-VEGF therapy should be halted in cases of RPE tear. Long-term visual outcomes with RPE tear are poor and vision decreases over time. Continued anti-VEGF therapy after the occurrence of an RPE tear has been reported to increase the size of tears, negatively impacting visual outcomes.

Paolo Lanzetta, University of Udine, Italy, observed that the most common association of RPE tear is nAMD, with OCT typically demonstrating a zone of RPE loss and an adjacent tented-up PED with a retracted and irregular RPE monolayer. Controversy exists among clinicians regarding the treatment criteria after the formation of RPE tears. He argued that clinicians should identify high-risk patients and be aware of strategies to prevent RPE tear development during anti-VEGF therapy. Continuing anti-VEGF treatment after RPE tear development is reasonable if based on the presence of disease activity and given that a functional benefit or stabilisation may be expected.

Professor Anat Loewenstein, Tel Aviv University, Israel, summarised the Vision Academy viewpoint on the management of RPE tear during anti-VEGF therapy (Table 3). After RPE tear develops and for unilobular lesions only, anti-VEGF therapy should be continued in most patients with active disease. An individualised approach is recommended, requiring careful and regular re-evaluation of retinal status and location of both tear and fluid.

Treat-and-extend regimen decisions should differentiate between intraretinal and subretinal fluid in nAMD

Prof Loewenstein noted that the aim of intravitreal anti-VEGF therapy for nAMD is to restore retinal anatomy to as close to normal as possible, that is, to achieve a 'dry' retina by elimination of both intraretinal and subretinal fluid. Therefore, there is no need to differentiate between IRF and SRF. Absence of retinal fluid is used as a measure of anti-VEGF treatment efficacy, and both IRF and SRF are indicators of ongoing disease activity. Treatment guidelines state that any fluid visualised on OCT is an indication of active disease. The risk of inducing GA when achieving a dry retina is overstated. Moreover, the ability to identify and differentiate residual fluid is operator-dependent. For example, in the HAWK phase 3 study, investigators identified the presence of either IRF or SRF in 16% of their patients, while disease activity was reported by the reading centre in 34% of patients [20].

Dr Lanzetta, University of Udine, Italy, said that the management of nAMD is increasingly shifting towards personalised protocols based on assessment of disease activity at each patient visit (i.e. loss of visual acuity (VA), new haemorrhage and presence of fluid on OCT). The norm has been to try to achieve absence of all retinal fluid on OCT, to return retinal anatomy to as close to normal as possible. He observed that the presence of baseline IRF is correlated with worse baseline VA and worse outcomes over time. Residual SRF on the other hand does not impact VA over time, and a zero-tolerance approach to SRF may not be required for optimal outcomes [21]. An association of residual SRF with improved VA was observed in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) study through year five [22]. Moreover, treatment regimens that aim to completely dry the macula require more frequent injections than approaches that tolerate some stable SRF. Analysis of a CATT cohort indicated that eyes treated monthly had a 59% higher risk of GA development than eyes treated as needed (P=0.003) [23]. The presence of IRF and the absence of SRF was found to be significantly associated with GA development (Table 4).

Treat-and-extend retreatment / extension decisions should differentiate between IRF and SRF to improve patient outcomes, argued Dr Lanzetta. While IRF results in worse outcomes for patients, some persistent SRF can be present without impacting visual outcomes. Suspending treatment in the presence of residual SRF can also reduce the risk of GA and decrease overall patient burden, he emphasised.

Viewpoint recommendations from the Vision Academy on the use of retinal fluid to guide individualised treatment regimens with anti-VEGF therapy for nAMD were presented by Dr Neil N Bressler, Johns Hopkins University School of Medicine, USA, and are summarised in Table 5.

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Table 3: Management of RPE tear during anti-VEGF therapy; Vision Academy* Viewpoint.

1. A multimodal retinal imaging approach is recommended for the diagnosis and monitoring of RPE tear
- RPE tears can be graded by size and foveal involvement

2. Patients at high risk of developing RPE tear should continue treatment but be monitored carefully (detailed examination after each injection is recommended)
- High risk for RPE tear is defined as the presence of one or more of the following risk factors at the onset of or during the course of anti-VEGF therapy
  - Increased surface area and large linear diameter of the subfoveal PED
  - A small ratio of CNV size to PED size
  - Serous vascularised PED (as compared to fibrovascular PED)
  - Presence of radial hyperreflective lines in patients with PED lesions
  - Recent PED (duration ≤4.5 months)
  - Microrips in the RPE
- The appearance of features that suggest the imminent development of RPE tear (e.g. 'wrinkling' on OCT or 'radial lines' on near-infrared reflectance imaging) could support the decision to stop treatment
  - Particularly in the presence of high-risk features or multilobular PED

3. After RPE tear develops, anti-VEGF treatment should be continued in most patients with active disease (as indicated by the presence of intra- or subretinal fluid)‡
- Suspension of anti-VEGF in cases of RPE tear in patients with active disease is not recommended as patients continue to show benefit with anti-VEGF therapy after a tear occurs
- An individualised approach is recommended, with careful and regular re-evaluation of retinal status and location of both tear and fluid

‡ This recommendation is for unilobular tears. Cessation of injections should be considered in patients with multilobular tears

4. Further considerations
- Progression of CNV lesion fibrosis can occur after RPE tear, resulting in reduced exudative activity
  - Patients should be carefully monitored and anti-VEGF treatment should be restarted if exudation recurs
  - Secondary fluid leakage can also occur in the absence of RPE
- In patients with larger (grade 4) tears, sustained treatment may help to stabilise and prevent further visual deterioration, although the prognosis in these patients is typically poor
  - Anti-VEGF treatment cannot restore the disrupted interface between the photoreceptors and the RPE following a tear
- Given the possible aetiology of RPE tears with the augmentation of CNV contraction, it is unclear whether changing the dosing schedule of anti-VEGF therapy reduces the incidence of RPE tear

Abbreviations: CNV, choroidal neovascularisation; OCT, optical coherence tomography; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

* The Vision Academy is a global collaboration of expert ophthalmologists and retinal specialists which seeks to provide guidance for best clinical practice in the management of retinal diseases, particularly in areas of controversy or with insufficient conclusive evidence. The Vision Academy is supported by Bayer.

Table 4: Development of geographic atrophy according to fluid status from an exploratory analysis of CATT.

	Patients at risk n	GA at Week 52 or 104 n (%)	Hazard ratio (95% CI)
Intraretinal fluid			
No fluid	261	26 (10.0)	1.00
Fluid not in foveal centre	272	46 (16.9)	1.82 (1.13 to 2.95)
Fluid in foveal centre	478	114 (23.8)	2.62 (1.71 to 4.01)
Subretinal fluid			
No fluid	164	54 (32.9)	1.00
Fluid not in foveal centre	492	81 (16.5)	0.45 (0.32 to 0.64)
Fluid in foveal centre	362	51 (14.1)	0.38 (0.26 to 0.56)

Abbreviations: CI, confidence interval; GA, geographic atrophy; IRF, intraretinal fluid; SRF, subretinal fluid.
Adapted from: Grunwald et al. [23].

Table 5: Vision Academy* Viewpoint: recommendations on the use of retinal fluid to guide treat-and-extend regimen decisions with anti-VEGF therapy for nAMD.

1. Differentiation of fluid types may help address discrepancies between visual and anatomical outcomes
- SRF is associated with better outcomes and may have a protective role, preventing atrophy1
- Persistent SRF does not impact visual outcomes in patients with treatment-naïve CNV2
- Baseline IRF is correlated with worse baseline visual acuity and worse outcomes3-5
- Persistent IRF results in decreased visual outcomes over time6

2. The presence of fluid (SRF, IRF and/or sub-RPE fluid) via OCT imaging should be recorded at baseline
3. Fluid compartments should be assessed individually and fluid status should be evaluated
- Patients should be examined on the first visit after the final loading dose for the presence of disease activity
  - If IRF and / or SRF levels are reduced, treatment should be continued until resolution is achieved
  - If there is no change in IRF or SRF levels (i.e., persistent IRF or persistent refractory SRF), the diagnosis should be re-evaluated with various methods, including fluorescein and indocyanine green angiography
  - Hyporeflective spaces exhibiting non-response to anti-VEGF treatment should be re-evaluated for atrophic spaces, loss of tissue, and / or retinal tubulations

4. Treatment intervals can be maintained or extended under the following circumstances
- Disease inactivity achieved
  - Absence of IRF and SRF
  - Absence of deterioration in vision attributable to CNV activity
  - Absence of retinal haemorrhage
  - Absence of leakage on fundus fluorescein angiography
- IRF is improving
- SRF is stable
  - Persistent refractory SRF (height of <200µm) without further decrease in response to treatment can be tolerated if observed in combination with additional signs of disease inactivity

5. Treatment intervals should be shortened under the following circumstances
- New and/or increased IRF, SRF or sub-RPE fluid
- IRF is not improving
  - Persistent IRF should be considered a biomarker of disease activity and is never tolerated

6. Further considerations
- While some persistent SRF can be tolerated, further studies are required to establish threshold values of SRF to help guide treatment decisions in clinical practice

Abbreviations: CNV, choroidal neovascularisation; IRF, intraretinal fluid; OCT, optical coherence tomography; SRF, subretinal fluid; sub-RPE, sub-retinal pigment epithelium; VEGF, vascular endothelial growth factor.

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