Measuring Inflammation in the Vitreous and Retina: A Narrative Review

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Abstract

Uveitis consists of a group of syndromes characterised by intraocular inflammation, accounting for up to 15% of visual loss in the western world and 10% worldwide. Assessment of intraocular inflammation has been limited to clinician dependent, subjective grading. Developments in imaging technology such as optical coherence tomography (OCT), have enabled the development of objective, quantitative measures of inflammatory activity. Important quantitative metrics including central macular thickness and vitreous signal intensity allow longitudinal monitoring of disease activity and can be used in conjunction with other imaging modalities enabling holistic assessment of ocular inflammation. Ongoing work into the validation of instrument-based measures alongside development of core outcome sets will be crucial for standardisation of clinical trial endpoints and developing guidance for quantitative multi-modal imaging approaches. This review outlines methods of grading inflammation in the vitreous and retina, with a focus on the use of OCT as an objective measure of disease activity.

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1. Introduction

Uveitis, characterised by intraocular inflammation, is a significant and potentially sight-threatening disease comprising a large, diverse group of individual syndromes. This major cause of ocular morbidity, predominantly affecting the working age population, accounts for up to 15% of visual loss in the western world and up to 10% worldwide.[1–4] These uveitis syndromes are classified anatomically into anterior, intermediate, posterior and pan- uveitis,[5,6] of which the most sight-threatening forms are those affecting the more posterior structures of the eye- intermediate, posterior and pan- uveitis.[7]

The burden of uveitis-associated disability is high, and there is keen interest in developing effective treatments, but there are a number of well-recognised challenges to the demonstration of effectiveness through clinical trials in uveitis, including the heterogeneity of disease (and consequent variation in which disease manifestation is of primary concern) and a lack of robust outcome measures for those disease manifestations.[7,8] The development of a core outcome set (COS) for non-infectious uveitis affecting the posterior segment has identified outcome measures representing the priorities of key stakeholders and includes crucial measures of disease activity in the vitreous and retina.[9] The development of the COS has also indicated that further work is still needed to identify the most appropriate methods of measuring key outcomes for assessment of *disease activity*. Historically, assessment of disease activity in uveitis has been confined to subjective, clinical measures some of which were successfully standardised by the Standardization of Uveitis Nomenclature (SUN) international workshop, which in 2005 developed semi-quantitative grading schema for anterior chamber (AC) cells, AC haze and vitreous haze.[5,10–12] Although these grading schema were a major step forward in standardising measures of inflammation, they are limited by being subjective estimates with significant variation in assessment by even experienced clinicians, with significant impact on their sensitivity when used as clinical trial outcomes.

Quantification of chorioretinal inflammation is even less well developed. There are no SUN grading scheme, although analogous schema have been proposed, such as the semiquantitative scoring system for the grading of posterior segment inflammation based on findings observed on dual fluorescein and indocyanine green angiography),[13] which had moderate to substantial interobserver agreement.[14]

Advances in technology have enabled the development of a range of novel imaging techniques enabling further progress towards objective, quantitative metrics. Optical coherence technology (OCT), first described in 1991, allows for noninvasive cross-sectional imaging at the microstructural level.[15] This imaging modality is now used worldwide in the diagnosis and monitoring of numerous ophthalmic diseases and can be employed to assess inflammation in anterior, intermediate and posterior structures of the eye.[16,17] Additionally, OCT angiography can be used to assess changes blood flow and detect uveitic complications such as inflammatory choroidal neovascularization[16]. OCT in conjunction with other imaging modalities such as traditional angiography, fundus photography and fundus autofluorescence are some of the techniques employed for multimodal imaging in uveitis to detect inflammatory activity and uveitic sequelae.[8,18] Current techniques allow for assessment of disease activity across the whole ocular axis, however most of these modalities are still interpreted subjectively such as assessment of inflammatory spots in white dot syndromes.[19]

The range of imaging modalities available shows promise for a transition to objective, instrument based quantification of inflammatory activity. Furthermore, ongoing development of automated, image based measures of disease activity involving key objective metrics has the potential to provide accessible, standardised outcome measures for use in clinical trials and day to day practice.[20,21] In this review, we aim to summarise techniques for the measurement of inflammatory activity in the vitreous and retina with an emphasis on OCT and progression to quantitative measures of disease.

2. Measuring inflammation in the vitreous

2.1. Clinical measures: Transition to quantitative grading

Inflammatory activity in the vitreous manifests as haze and opacities, described by Kimura et al in 1959.[11] These changes occur secondary to inflammatory cells, tissue debris and protein exudation permeating the vitreous. Opacities are classified into fine, coarse, stringy and snowball opacities, of which the latter can coalesce to form a snowbank typically seen in the inferior vitreous base and ora serrata.[11,22] The measurement of vitreous haze is regarded as the critical measure of inflammation in the vitreous, and has been adopted in uveitis clinical trials for several decades.

Clinical measures of vitreous haze and cells depend on the observer's semi-quantitative estimate of the level of obscuration of fundus details.[5,8,11,12] Originally, Kimura et al. measured retrolental vitreous cells and black dots by retroillumination. Nussenblatt et al. adapted the Kimura approach to an ordinal scale ranging from 0 (0 to 1 vitreous cells, or clear vitreous) to 4+ (>251 vitreous cells or dense opacities) using a slit-lamp with Hruby contact lens.[11] This measure provided the first step in standardising measures of inflammation in the vitreous. However, they and others recognized that retrolental number of cells had limitations as a measure of inflammatory activity marker, since vitreous inflammatory cells and debris are difficult to differentiate and may persist in inactive eyes. A major step forward was the use of the indirect ophthalmoscope with 20 Dioptre lens described by Nussenblatt et al, leading to the National Eye Institute six-step vitreous haze scale. This scale has been endorsed by the SUN international workshop in 2005, with the amendment that the designation "trace" be calculated as 0.5+ to ensure a fully quantitative scale.[5] This development of a quantitative grading scale facilitates standardised measurement in clinical practice, which in turn permits longitudinal comparison to assess whether inflammation is worsening or improving, and is critical to rational treatment decisions in practice or assessment of the effect or a novel intervention in clinical trials.[8]

The reliability of clinical grading of inflammation remains limited by its subjective nature, being dependent on the estimation of the clinician. To support standardisation, Nussenblatt et al provided a reference set of photographs for their 6-step scale illustrating the fundal view in different grades of vitreous haze.[12] Even so the interobserver reproducibility is limited, with only moderate interobserver agreement of k=0.53 for the exact grade, and k=0.75 for agreement within 1 grade.[23] A further disadvantage is that the scale is not continuous, but consists of discrete, broad steps between grades, with the lower end of the scale being unequal. This means that the continuity of measurement is limited and the scale is particularly insensitive for grading the milder levels of vitreous haze more commonly seen in ocular inflammation.

The use of grading scales in quantifying inflammation has clear benefits as illustrated by their wide use in routine practice and as outcome measures in clinical trials, but their limitations are well recognised and their is long-standing interest in the development of novel, instrument-based tools that could bring objectivity, increased reliability and potentially other advantages such as automation.[8,24,25] The response to these limitations in the context of vitreous haze has been the development of image-based objective measures of vitreous haze quantification, a potential paradigm shift in the evolution of inflammatory grading.

2.2. OCT: Transition to objective, instrument based, automated vitreous analysis

An FDA/NEI workshop in 2015 highlighted the limitations in the assessment of uveitis, its implications for clinical trials, and identified key markers of inflammation in uveitis for which reliable outcome measures were required for clinical trials in uveitis.[8] Vitreous haze was selected as one of these priority outcomes, but with recognition that there was a need for a more objective, reliable way of measuring this than clinical assessment. To date, the most promising imaging modality that addresses this need is OCT with ongoing research into its use as a marker of inflammation.[8,26–30]

Spectral domain optical coherence tomography (SD-OCT), the most commonly used OCT technology, derives structural features based on the interaction of light with ocular tissues.[16]

The presence of vitreous cells and vitreous haze can be detected by SD-OCT. With regard to cells, Masaaki et al reported a pilot study involving 7 patients with ocular inflammation, in which they showed that reported that cells in the posterior vitreous could not only be imaged but counted to detect changes in inflammation.[31] In this regard, manual count of hyperreflective dots in the supramacular vitreous cavity through high-definition-Swept-Source optical coherence tomography (SS-OCT) scans was significantly higher in eyes with active inflammation than in inactive or healthy eyes. However, it was significantly higher in inactive uveitis eyes than in healthy controls as well. Moreover, the correlation of this marker with global intraocular inflammation assessment and NEI vitreous haze scale was poor and non-significant.[32] The use of OCT vitreous signal intensity as an instrument-derived measure of vitreous haze was first described by Keane et al in 2014.[26] Macula-centred OCT scans were manually segmented using custom software "OCTOR" and pixel intensity summed to derive a mean OCT intensity.[33] The vitreous (Vit) and retinal pigment epithelium (RPE) mean intensities were calculated to yield a Vit:RPE-relative intensity ratio. This method of measurement was able to differentiate between the presence and absence of vitreous haze and showed significant, positive correlation (r=0.566, p=0.0001) with NEI vitreous haze grading. Measurement of "absolute" vitreous signal intensity reflects the mean intensity of image pixels in the vitreous compartment on OCT images. This value independently can be prone to the effects of confounding factors such as anterior media opacities and OCT signal strength. The authors proposed that comparison with RPE intensity as a reference value allows for mitigation of these confounding factors. Further validation of this technique shows that automated quantification of vitreous intensity is reliable, has sufficient tolerance for variation in image acquisition operator factors and is not influenced by factors affecting media clarity such as phakic status and previous vitrectomy.[20,30,34,35] The potential of Vit:RPE index use as a quantitative endpoint for monitoring disease activity longitudinally was illustrated by Sreekantam et al who found that improvement in Vit:RPE indices was significantly correlated with a reduction in central retinal thickness (CC=0.534, p=0.011) and improvement in visual acuity (CC=0.702, p=0.0001) for patients receiving sub-tenon's triamcinolone for uveitic cystoid macular oedema (CMO).[29] This is the first study investigating 'treatment-response' using an

OCT based measure of vitreous haze. Although the sample size was small (n=22), the investigation detected a highly statistically significant change in vitreous haze post treatment (p=0.00003). This longitudinal quantification using a novel OCT parameter shows significant potential as an objective marker of disease activity and treatment response. Furthermore, this method of instrument-based vitreous analysis utilises routinely collected imaging data, illustrating its possible implementation in clinical practice.

There are two main limitations with this method of quantification. The first is the requirement for manual segmentation. The introduction of automated solutions has however addressed this, greatly accelerating the speed with which scans can be analysed.[28] The second important limitation with Vit:RPE index usage is that factors disrupting the RPE (e.g. CMO, choroidal neovascular membrane) can affect the RPE intensity, affecting the overall ratio.

2.3. Additional techniques

Alternative methods of instrument based quantification of vitreous inflammation include ultrasound biomicroscopy (UBM) and retinal photography.[27,36–41] UBM can be utilised to assess the ocular axis from the anterior uvea, to the vitreous base and peripheral retina. Studies using a range of UBM probes demonstrated the feasibility of using this modality in vitreous assessment to detect changes such as vitreoretinal traction and snowbanking.[36–38] The main limitations associated with UBM are firstly, interpretation of the images is qualitative and operator dependent. Secondly, UBM is not as readily available in eye clinics, with OCT being the more widely chosen modality.

As described earlier, the use of colour fundus photography has been evaluated by Davis et al, who developed a 9-stage grading scale (the Miami scale) for digitised images.[39,40] The advantage of this method is that lower levels of vitreous haze can be graded, and the interval between steps is reduced, allowing for potentially higher sensitivity in detecting smaller changes in vitreous haze. As discussed, the main limitation with such measures is the subjective grading component dependent on clinician judgement. Passaglia et al developed an algorithm based grading system which showed a strong correlation with expert graders (exact: $\kappa = 0.71$;

within-one grade: κ = 0.79; within-two grades: κ = 0.82) assessing vitreous haze on fundus photographs using the NEI scale.[41] The authors describe an algorithm that is applied to fundus photographs to yield quantitative measures of vitreous haze, and can be used with any existing images. This provides a promising method of vitreous haze measurement using fundus photographs without the element of subjectivity. It should be recognised however that none of these techniques currently deal with detecting and compensating for opacities that are anterior to the vitreous, and which may falsely increase the estimated vitreous haze.

In summary, the vitreous remains an essential but challenging indicator of the inflammatory status of the eye. OCT assessment of vitreous haze shows the most promising results thus far for instrument based, objective quantification of disease activity. This routinely collected imaging modality enables longitudinal tracking of inflammatory activity and is crucial in the transition to automated, quantitative disease measures.

3. Measuring inflammation in the retina

3.1. Clinical measures: scope and limitations of examination based assessment

Uveitis with posterior segment involvement comprises intermediate, posterior and pan-uveitis. These disease entities have the potential to cause lasting damage to photosensitive ocular structures and supplying tissues, and have the highest risk of sight-loss. Inflammation can manifest posteriorly as macular oedema, choroidal and/or retinal infiltrates, retinal vasculitis and optic nerve changes.[11,42] With the exception of macular oedema (where quantification with OCT is well-established) the measurement of these changes is challenging in both routine practice and clinical trial settings.

3.2. OCT: 3D evaluation of retinal structure

OCT enables thorough assessment of the retinal layers allowing for instrument based qualitative and quantitative measures of disease activity. This section summarises the application of OCT to detect important structural changes in uveitis with posterior segment involvement. Posterior uveitis findings which are more readily evaluated with imaging modalities other than OCT are described later in this review.

3.2.1. Macular edema

Macular edema (ME) is a common and significant complication of uveitis with a high risk of visual loss.[43,44] Prior to the development of OCT, the mainstay of assessment for ME was biomicroscopy and fluorescein angiography. Both of these methods of assessment are not easily quantifiable, and it is often difficult to appreciate ME on biomicroscopy alone. OCT enabled more reliable diagnosis and monitoring of ME through its ability to acquire a quasi-histological, cross-sectional representation of the retinal layers. OCT can provide non-invasive images for qualitative assessment to differentiate between the three major patterns of uveitic ME, namely cystoid macular edema (CME), diffuse macular edema and serous retinal detachment.[45] Standard OCT user interfaces can also, equally importantly, output quantitative metrics such as retinal thickness which can be used to track fluid accumulation sequentially.[46,47] Central macular thickness (CMT) on OCT scans is negatively correlated with VA, with a 20%

change in thickness being considered clinically significant.[45,46] Additional measures of visual function including reading VA and reading speed have also been linked to structural change seen on OCT.[48,49]

Although OCT has been successfully used to longitudinally assess ME in clinical trials and in practice, there are a number of remaining limitations and challenges. Firstly, there is still considerable variation in what metric is used and how it is reported. Reporting of OCT changes includes outcomes ranging from straightforward binary threshold based classification (presence/absence of ME), to change in CMT as a log score.[46,50–52] This limits comparability of individual studies emphasizing the need for standardised reporting measures.[9] Secondly, a single OCT-derived metric (such as the commonly used CMT) may not detect small or slightly eccentric changes in inflammatory activity which do not cause volume induced displacement of the retinal layers in the measured area. Thirdly, it must always be remembered that OCT is measuring structure and is static, providing evidence of the presence of oedema but not about whether this is actively leaking or not; for detection of dye leakage we remain dependent on traditional fundus fluorescein angiography (FFA). ME may be visible on OCT without active leakage on FFA, and vice versa. Both approaches therefore have a distinct role, although the convenience, safety and quantification possible through OCT make it much the more commonly used technique in contemporary practice.[53–56] In addition, previous studies have reported that CMT is significantly higher than normal in uveitic eyes with active inflammation.[57]

3.2.2. Retinal and choroidal inflammation

Inflammation of the retina and choroid can manifest funduscopically as various patterns of greyish-white spots representing infiltrates of inflammatory cells, larger areas of diffuse inflammation, or associated inflammatory changes of the retinal vasculature. Importantly however they may be 'invisible' if they lie deeper into the choroid. Furthermore, coexisting healed and actively inflamed lesions are common. Non-invasive imaging (OCT, fundus autofluorescence) and/or Invasive dye-based imaging techniques are necessary to assess chorioretinal inflammation status accurately in the vast majority of posterior and panuveitis.

Clinical classifications include features such as how well circumscribed they are and relative depth (Kimura et al) or the specific layer(s) involved and their number (SUN classification).[11] Overall however, the information contained by the clinical appearance alone is limited with considerable overlap between uveitis syndromes that are increasingly recognised as distinct phenotypes.

OCT is critical when assessing inflammation of the retinal and choroid. Alongside a fundus photograph, it forms the centre-piece of the multimodal imaging approach to the reliable assessment of uveitis which includes, as needed, fundus autofluorescence, FFA and indocyanine green angiography. OCT provides information regarding the substructure of lesions affecting the posterior pole predominantly but has also been shown promising results in extramacular enhanced depth imaging in chorioretinal assessment.[58] The retinal substructure can be seen in various white dot syndromes as hyperreflectivity of the outer retinal layers and disruption of the ellipsoid zone.[59,60] Posterior uveitis syndromes such as Multiple Evanescent White Dot Syndrome, Birdshot Chorioretinopathy and punctate inner choroidopathy (PIC) have characteristic differentiating features on imaging.[16,61,62] An example of this is the disintegration of the photoreceptor inner segment/ outer segment boundaries and dome-shaped hyperreflectivity in PIC.[19,63,64] These characteristics are better differentiated using multi-modal imaging than singular techniques.

The benefit of OCT in the management of posterior uveitis is already evident, for example the use of OCT based retinal thickness maps for the assessment of PIC allows for quantitative analysis of average change in various parts of the macular grid.[64] Madhusudhan et al used these thickness maps to demonstrate resolution of active PIC lesions following intravitreal triamcinolone.[64] The retina can be readily evaluated by SD-OCT however this OCT technique has limited use for choroidal assessment due to signal attenuation in deeper structures. Newer technologies such as enhanced depth OCT and swept source OCT are able to provide higher quality imaging of the choroid to monitor certain types of uveitides, with SS-OCT also providing better scan signaling in hazy vitreous.[65–68] The use of thickness maps for a range of relevant

structures (perivascular, macular, peripapillary, subretinal and intraretinal foci or fluid) can be used as indirect signs of chorioretinal inflammation in an holistic way.[32,69] There are however challenges. For example, the limited scanning frame of *en face* thickness maps and the challenge of differentiating whether persistent thickening of structures in uveitis is due to active inflammation or established complications ('damage'). Nevertheless, the various OCT technologies that are now available have the capacity to monitor disease activity in addition to associated complications or damage, and provide key information to inform treatment decisions.

Choroidal thickness has been investigated as an active inflammation marker in posterior uveitis, and in stromal choroiditis in particular.[70–72] Subfoveal choroidal thickness can be manually measured in transfoveal B-scans obtained through SD-OCT Enhanced Deep Imaging mode, or automatically segmented in SS-OCT devices, providing a sectoral ETDRS-grid choroidal thickness map. Sclero-choroidal boundary is sometimes erroneously segmented by automated algorithms, especially when the scan signal is poorer, so manual correction is frequently required. Unfortunately, choroidal thickness is highly variable in healthy and affected eyes, depending on the eye axial length, sex, refraction, circadian oscillation, ethnicity and age. Thus, despite being a good longitudinal measure of inflammation in a particular patient, its generalisability is limited. Its correlation with an averaged thickened retinal index (ATR, from thickness maps analysis) was good, but with global intraocular inflammation was only fair. Moreover, the mean choroidal thickness was not significantly different between eyes with active uveitis of various etiologies and matched inactive or healthy control eyes.[32]

3.2.3. Retinal nerve fibre layer thickening

Inflammatory disc edema, or papillitis, can occur in all anatomical types of uveitis.[4] This swelling can be appreciated on clinical examination and subjectively quantified,[11] however more reliable assessment with OCT and fluorescein angiography enables objective quantification and delineation of the character of papillitis.[73–76] Whilst dedicated OCT of the optic nerve head is unusual in the uveitis clinic, longitudinal retinal nerve fibre layer thickness which is commonly

performed in in the uveitis clinics often picks up these same changes. RNFL thickening therefore provides another potential objective, longitudinal measure of disease acitivity.[77,78]

3.3. Additional techniques: Multimodal imaging

Multimodal imaging is a crucial concept in detection and monitoring of uveitis involving the posterior segment including white dot syndromes. Combining OCT with imaging modalities such as fundus autofluorescence, wide-field technologies and angiography provides valuable structural information to guide the management of patients with uveitis.

En-face imaging techniques including fundus autofluorescence (FAF), near-infrared (NIR)[62,79] and wide-field imaging can be employed to assess 2-dimensional qualities of retinal lesions. FAF relies autofluorescence of pigments such as lipofuscin, which in oxidative cellular damage, can accumulate in the retinal pigment epithelium.[80] The excessive accumulation of lipofuscin is detected on FAF as hyperfluorescence and can be associated with several types of posterior uveitis.[81,82] Hyper/hypo-autofluorescence can signify changes in inflammatory activity in addition to providing insights into pathogenesis of white dot syndromes.[81,83–85] Investigation of spatial agreement between Goldmann visual field (GVF) and FAF defects demonstrated the value of FAF in detecting anatomic change.[86] FAF images are interpreted subjectively by clinicians, however Boudreault et al demonstrated the use of quantitative autofluorescence (qAF) using a confocal scanning laser ophthalmoscope equipped with an internal fluorescent reference.[87] The use of qAF showed elevated intensities in patients with acute zonal occult outer retinopathy compared to matched controls. Combination of FAF and infrared imaging with subsequent automated segmentation of lesions in PIC has been demonstrated by Ometto et al.[21] This allows for measurement of the total area of atrophic lesions and furthermore, the rate of expansion. This combination of multimodal imaging with automated segmentation to output quantitative metrics can be considered the next milestone in measuring inflammation in the retina.

Whilst the imaging modalities described enable assessment of various disease outcomes, changes in blood vessel characteristics are equally important in inflammatory disease. The three types of angiography allow for evaluation of changes such as vasculitis and vessel leakage, vessel nonperfusion, neovascularization, and edema. Currently available angiography techniques include: FFA, Indocyanine green angiography (ICGA) and OCT angiography (OCTA). FFA, developed in the 1960s provided significant advancement in the analysis of retinal blood flow to test for neovascularization, nonperfusion and vessel inflammation.[88] ICGA was developed later on in the 1990s and provides better imaging of the choroid compared to FA, due to its ability to fluoresce in the infrared wavelengths.[74] Both ICGA and FA have been used extensively in the assessment of posterior uveitis and detection of associated neovascularization.[74,89–91] The main limitation associated with these two angiographic modalities are their invasiveness. Both types involve the injection of a dye into the bloodstream which can then be used to analyse blood flow, and vessel leakage. The use of dye carries the risk of anaphylactic shock which is life-threatening. OCTA involves the use of OCT technology to detect the change between consecutive scans, interpreted as blood flow.[92] This technique is completely non-invasive, and its use in detection of vascular flow abnormalities and neovascularization has been demonstrated in patients with uveitis.[16,82,91] The main benefit of using traditional angiography over OCTA is that OCTA is unable to detect vascular leakage due to the lack of an intravascular dye.[91] In addition to qualitative data, OCTA imaging can generate quantitative metrics such as vessel density, fractal dimension and foveal avascular zone area.[93–97] This relatively new angiographic technology allowing rapid, high resolution imaging shows potential to be incorporated into routine care with traditional methods of angiography being reserved for specific use cases in the future.

In summary, multi-modal imaging including OCT, represents a key milestone in the assessment of retinal inflammation in clinical practice, and in the development of surrogate endpoints in clinical trials. The application of machine learning techniques to image analysis, classification and automated quantification of structural change is imminent and likely to transform the

monitoring of uveitis, particularly the diagnosis and monitoring of inflammatory changes of the retina and choroid.

3.4 Looking to the future: integrated, whole-eye approaches to assessing intraocular inflammation

One of the challenges of assessing uveitis over time is that it may not fit neatly into one anatomical subtype, and indeed the anatomical site of predominant inflammation may change over time.[98] Over the years a number of composite measures of inflammation have been proposed,[99,100] such as Pato et al's uveitis disease activity index (UVEDAI).[101] Most of these have continued to be dominated by clinically assessed features, with minimal use of objective, instrument-based measures with the exception of OCT for macular oedema.[101]

The aspiration is however to move to a holistic approach which combines 'whole eye' instrument-based assessment of inflammation with patient-reported outcome measures.[101,102] Recent work from Llorenc et al describes an intraocular inflammation composite score based on four anterior and posterior segment image acquisition protocols per eye using SS-OCT. They studied 224 eyes with uveitis (165 active and 59 inactive) and 38 eyes from 19 healthy controls. SS-OCT-derived biomarkers were ranked based on discriminatory power, with clinician assessment being the reference standard. The most discriminating SS-OCT biomarkers were the number of anterior chamber hyperreflective dots (anterior), high-definition vitreous intensity index (intermediate) and averaged thickened retinal index (posterior). The composite score was highly discriminant between active and inactive, and between active and healthy eyes (means 2.06 SD 1.86, 0.93 SD 0.44, and 0.96 SD 0.38, respectively, both p -, Mann-Whitney U). Further validation would include sensitivity to change analysis and wider multicentric evaluation. Whilst these 'whole eye' approaches are attractive, there are challenges about turning this into a single composite score including how the relative contributions (e.g from different parts of the eye) should be weighted. Having a single index of activity may be valuable, but needs to be

accompanied by those measures of site-specific disease activity on which it is based so as to support better, targeted treatment decisions.

4. Conclusion

The advent of OCT has revolutionised ophthalmic practice through its ability to provide high resolution, non-invasive imaging of the whole ocular axis. OCT, as a key technique in multimodal imaging, yields important qualitative and quantitative data to measure inflammatory activity in the retina and vitreous. The importance of standardised and comparable measures of inflammation is clear, which prompted the transition from qualitative assessment, to semi-quantitative grading scales. This represented the first shift in practice towards the end goal of biologically and functionally relevant surrogate markers of disease. The key challenge with clinical grading scales is their subjective, clinician dependent nature which results in interobserver variation. Additionally, clinical assessment is unable to capture certain aspects of inflammatory changes such as retinal structure, fluid accumulation, vascular leakage and accurate assessment of longitudinal progression of chorioretinal lesions. The introduction of multimodal imaging including OCT represents the second shift in measuring inflammation with the potential for objective, instrument based measures of disease. The next steps in forming reliable surrogate markers of disease are already underway, with a focus on developing methods of image quantification through existing metrics, but also algorithm oriented novel techniques. In conjunction with the development of core outcome sets in uveitis, the benefits of instrument based measures in broad terms are two fold. First, these objective, quantitative measures of disease enable direct comparison of studies using reliable, relevant endpoints in clinical trials. Second, clinicians will have more reliable tools for early detection of inflammatory exacerbations and to guide decisions surrounding the choice and timing of treatments. This third transition in grading inflammation, towards automated, image based measures of disease has the potential to significantly enhance both drug development and clinical practice.

References

1. Durrani OM, Meads CA, Murray PI. Uveitis: A potentially blinding disease. *Ophthalmologica*. 2004;218(4):223-236. doi:10.1159/000078612

2. Williams GJ, Brannan S, Forrester JV, et al. The prevalence of sight-threatening uveitis in Scotland. *Br J Ophthalmol*. 2007;91(1):33-36.

3. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California: The Northern California Epidemiology of Uveitis Study. *Ophthalmology*. 2004;111(3):491-500.

4. Jones NP. The Manchester Uveitis Clinic: The First 3000 Patients—Epidemiology and Casemix. *Ocul Immunol Inflamm*. 2015;23(2):118-126.

5. Jabs DA, Nussenblatt RB, Rosenbaum JT, et al. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140(3):509-516.

6. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol*. 1987;103(2):234-235.

7. Denniston AK, Holland GN, Kidess A, et al. Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior, and panuveitis. *Orphanet Journal of Rare Diseases*. 2015;10(1). doi:10.1186/s13023-015-0318-6

8. Denniston AK, Keane PA, Srivastava SK. Biomarkers and Surrogate Endpoints in Uveitis: The Impact of Quantitative Imaging. *Investigative ophthalmology & visual science*. 2017;58(6):BIO131-BIO140. doi:10.1167/iovs.17-21788

9. Tallouzi MO, Mathers JM, Moore DJ, et al. Development of a Core Outcome Set for Clinical Trials in Non-infectious Uveitis of the Posterior Segment. *Ophthalmology*. Published online January 28, 2021. doi:10.1016/j.ophtha.2021.01.022

10. Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. *Am J Ophthalmol*. 1959;47(5 Pt 2):155-170.

11. Kimura SJ, Thygeson P, Hogan MJ. Signs and symptoms of uveitis. II. Classification of the posterior manifestations of uveitis. *Am J Ophthalmol*. 1959;47(5 Pt 2):171-176.

12. Nussenblatt RB, Palestine AG, Chan C-C, Roberge F. Standardizatlon of Vitreal inflammatory Activity in Intermediate and Posterior Uveitis. *Ophthalmology*. 1985;92(4):467-471.

13. Tugal-Tutkun I, Herbort CP, Khairallah M, Angiography Scoring for Uveitis Working Group (ASUWOG). Scoring of dual fluorescein and ICG inflammatory angiographic signs for the grading of posterior segment inflammation (dual fluorescein and ICG angiographic scoring system for uveitis). *Int Ophthalmol*. 2010;30(5):539-552.

14. Tugal-Tutkun I, Herbort CP, Khairallah M, Mantovani A. Interobserver agreement in scoring

of dual fluorescein and ICG inflammatory angiographic signs for the grading of posterior segment inflammation. *Ocul Immunol Inflamm*. 2010;18(5):385-389.

15. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254(5035):1178-1181.

16. Invernizzi A, Cozzi M, Staurenghi G. Optical coherence tomography and optical coherence tomography angiography in uveitis: A review. *Clin Experiment Ophthalmol*. 2019;47(3):357-371.

17. Onal S, Tugal-Tutkun I, Neri P, P Herbort C. Optical coherence tomography imaging in uveitis. *Int Ophthalmol*. 2014;34(2):401-435.

18. Marchese A, Agarwal A, Moretti AG, et al. Advances in imaging of uveitis. *Ther Adv Ophthalmol*. 2020;12:2515841420917781.

19. Knickelbein JE, Sen N. *Multimodal Imaging of the White Dot Syndromes and Related Diseases*. Vol 7. NIH Public Access; 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4959777/

20. Terheyden JH, Ometto G, Montesano G, et al. Automated quantification of posterior vitreous inflammation: optical coherence tomography scan number requirements. *Sci Rep*. 2021;11(1):3271.

21. Ometto G, Montesano G, Sadeghi Afgeh S, et al. Merging Information From Infrared and Autofluorescence Fundus Images for Monitoring of Chorioretinal Atrophic Lesions. *Transl Vis Sci Technol*. 2020;9(9):38.

22. Bonfioli AA, Damico FM, Curi ALL, Orefice F. Intermediate uveitis. *Semin Ophthalmol*. 2005;20(3):147-154.

23. Kempen JH, Ganesh SK, Sangwan VS, Rathinam SR. Interobserver agreement in grading activity and site of inflammation in eyes of patients with uveitis. *Am J Ophthalmol*. 2008;146(6):813-818.e1.

24. Herbort CP Jr, Tugal-Tutkun I, Neri P, Pavésio C, Onal S, LeHoang P. Failure to Integrate Quantitative Measurement Methods of Ocular Inflammation Hampers Clinical Practice and Trials on New Therapies for Posterior Uveitis. *J Ocul Pharmacol Ther*. 2017;33(4):263-277.

25. Herbort CP, Tugal-Tutkun I. The importance of quantitative measurement methods for uveitis: laser flare photometry endorsed in Europe while neglected in Japan where the technology measuring quantitatively intraocular inflammation was developed. *Int Ophthalmol*. 2017;37(3):469-473.

26. Keane PA, Karampelas M, Sim DA, et al. Objective measurement of vitreous inflammation using optical coherence tomography. *Ophthalmology*. 2014;121(9):1706-1714.

27. Liu X, Hui BTK, Way C, et al. Noninvasive Instrument-based Tests for Detecting and Measuring Vitreous Inflammation in Uveitis: A Systematic Review. *Ocul Immunol Inflamm*. Published online October 6, 2020:1-12.

28. Keane PA, Balaskas K, Sim DA, et al. Automated Analysis of Vitreous Inflammation Using Spectral-Domain Optical Coherence Tomography. *Transl Vis Sci Technol*. 2015;4(5):4.

29. Sreekantam S, Macdonald T, Keane PA, Sim DA, Murray PI, Denniston AK. Quantitative analysis of vitreous inflammation using optical coherence tomography in patients receiving sub-Tenon's triamcinolone acetonide for uveitic cystoid macular oedema. *British Journal of Ophthalmology*. 2017;101(2):175-179. doi:10.1136/bjophthalmol-2015-308008

30. Zarranz-Ventura J, Keane PA, Sim DA, et al. Evaluation of Objective Vitritis Grading Method Using Optical Coherence Tomography: Influence of Phakic Status and Previous Vitrectomy. *Am J Ophthalmol*. 2016;161:172-180.e1-e4.

31. Saito M, Barbazetto IA, Spaide RF. Intravitreal cellular infiltrate imaged as punctate spots by spectral-domain optical coherence tomography in eyes with posterior segment inflammatory disease. *Retina*. 2013;33(3):559-565.

32. Llorenç V, Serrano AR, Mesquida M, et al. Swept-source optical coherence tomography objective composite activity score for uveitis. *Acta Ophthalmol*. 2021;(aos.14739). doi:10.1111/aos.14739

33. Sadda SR, Keane PA, Ouyang Y, Updike JF, Walsh AC. Impact of scanning density on measurements from spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2010;51(2):1071-1078.

34. Montesano G, Way CM, Ometto G, et al. Optimizing OCT acquisition parameters for assessments of vitreous haze for application in uveitis. *Sci Rep*. 2018;8(1):1648.

35. Lee H, Kim S, Chung H, Chan Kim H. Automated Quantification of Vitreous Hyperreflective Foci and Vitreous Haze Using Optical Coherence Tomography in Uveitis Patients. *Retina*. Published online April 12, 2021. doi:10.1097/IAE.0000000000003190

36. Doro D, Manfrè A, Deligianni V, Secchi AG. Combined 50- and 20-MHz Frequency Ultrasound Imaging in Intermediate Uveitis. *Am J Ophthalmol*. 2006;141(5):953-955. doi:10.1016/j.ajo.2005.11.048

37. Häring G, Nölle B, Wiechens B. Ultrasound biomicroscopic imaging in intermediate uveitis. *Br J Ophthalmol*. 1998;82(6):625-629.

38. Oksala A. Ultrasonic findings in the vitreous space in patients with detachment of the retina. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1977;202(3):197-204.

39. Davis JL, Madow B, Cornett J, et al. Scale for photographic grading of vitreous haze in uveitis. *Am J Ophthalmol*. 2010;150(5):637-641.e1.

40. Madow B, Galor A, Feuer WJ, Altaweel MM, Davis JL. Validation of a photographic vitreous haze grading technique for clinical trials in uveitis. *Am J Ophthalmol*. 2011;152(2):170-176.e1.

41. Passaglia CL, Arvaneh T, Greenberg E, Richards D, Madow B. Automated Method of Grading Vitreous Haze in Patients With Uveitis for Clinical Trials. *Transl Vis Sci Technol*. 2018;7(2):10. doi:10.1167/tvst.7.2.10

42. Wintergerst MWM, Liu X, Terheyden JH, et al. Structural Endpoints and Outcome Measures in Uveitis. *Ophthalmologica*. Published online June 1, 2021. doi:10.1159/000517521

43. Rothova A, Suttorp-Van Schulten MSA, Treffers F, et al. *Causes and Frequency of Blindness in Patients with Intraocular Inflammatory Disease*. Vol 80.; 1996:332-336.

44. Accorinti M, Okada AA, Smith JR, Gilardi M. Epidemiology of Macular Edema in Uveitis. *Ocul Immunol Inflamm*. 2019;27(2):169-180.

45. Markomichelakis NN, Halkiadakis I, Pantelia E, et al. Patterns of macular edema in patients with uveitis: qualitative and quantitative assessment using optical coherence tomography. *Ophthalmology*. 2004;111(5):946-953.

46. Sugar EA, Jabs DA, Altaweel MM, et al. Identifying a Clinically Meaningful Threshold for Change in Uveitic Macular Edema Evaluated by Optical Coherence Tomography. *Am J Ophthalmol*. 2011;152(6):1044-1052.e5. doi:10.1016/j.ajo.2011.05.028

47. Hee MR, Puliafito CA, Wong C, et al. Quantitative assessment of macular edema with optical coherence tomography. *Arch Ophthalmol*. 1995;113(8):1019-1029.

48. Kiss CG, Barisani-Asenbauer T, Maca S, Richter-Mueksch S, Radner W. Reading performance of patients with uveitis-associated cystoid macular edema. *Am J Ophthalmol*. 2006;142(4):620-624.

49. Munk M, Kiss C, Huf W, et al. Therapeutic interventions for macular diseases show characteristic effects on near and distance visual function. *Retina*. 2013;33(9):1915-1922.

50. Kempen JH, Altaweel MM, Holbrook JT, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. *Ophthalmology*. 2011;118(10):1916-1926.

51. Bélair M-L, Kim SJ, Thorne JE, et al. Incidence of Cystoid Macular Edema after Cataract Surgery in Patients with and without Uveitis Using Optical Coherence Tomography. *Am J Ophthalmol*. 2009;148(1):128-135.e2. doi:10.1016/j.ajo.2009.02.029

52. Lowder C, Belfort R Jr, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545-553.

53. Antcliff RJ, Stanford MR, Chauhan DS, et al. Comparison between optical coherence tomography and fundus fluorescein angiography for the detection of cystoid macular edema in patients with uveitis. *Ophthalmology*. 2000;107(3):593-599.

54. Ossewaarde-van Norel J, Camfferman LP, Rothova A. Discrepancies between fluorescein angiography and optical coherence tomography in macular edema in uveitis. *Am J Ophthalmol*. 2012;154(2):233-239.

55. Kempen JH, Sugar EA, Jaffe GJ, et al. Fluorescein angiography versus optical coherence tomography for diagnosis of uveitic macular edema. *Ophthalmology*. 2013;120(9):1852-1859.

56. Suhler EB, Smith JR, Wertheim MS, et al. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol*. 2005;123(7):903-912.

57. Kim M, Choi SY, Park Y-H. Analysis of choroidal and central foveal thicknesses in acute

anterior uveitis by enhanced-depth imaging optical coherence tomography. *BMC Ophthalmol*. 2017;17(1):225.

58. Keane PA, Allie M, Turner SJ, et al. Characterization of birdshot chorioretinopathy using extramacular enhanced depth optical coherence tomography. *JAMA Ophthalmol*. 2013;131(3):341-350.

59. Goldenberg D, Habot-Wilner Z, Loewenstein A, Goldstein M. Spectral domain optical coherence tomography classification of acute posterior multifocal placoid pigment epitheliopathy. *Retina*. 2012;32(7):1403-1410.

60. Gallagher MJ, Yilmaz T, Cervantes-Castañeda RA, Foster CS. The characteristic features of optical coherence tomography in posterior uveitis. *Br J Ophthalmol*. 2007;91(12):1680-1685.

61. Pichi F, Invernizzi A, Tucker WR, Munk MR. Optical coherence tomography diagnostic signs in posterior uveitis. *Prog Retin Eye Res*. 2020;75:100797.

62. Zicarelli F, Mantovani A, Preziosa C, Staurenghi G. Multimodal Imaging of Multiple Evanescent White Dot Syndrome: A New Interpretation. *Ocul Immunol Inflamm*. 2020;28(5):814-820.

63. Chen S-N, Hwang J-F. Ocular coherence tomographic and clinical characteristics in patients of punctuate inner choroidopathy associated with zonal outer retinopathy. *Ocul Immunol Inflamm*. 2014;22(4):263-269.

64. Madhusudhan S, Keane PA, Denniston AK. Adjunctive use of systematic retinal thickness map analysis to monitor disease activity in punctate inner choroidopathy. *J Ophthalmic Inflamm Infect*. 2016;6(1). doi:10.1186/s12348-016-0073-4

65. Invernizzi A, Mapelli C, Viola F, et al. CHOROIDAL GRANULOMAS VISUALIZED BY ENHANCED DEPTH IMAGING OPTICAL COHERENCE TOMOGRAPHY. *Retina*. 2015;35(3):525-531. doi:10.1097/iae.0000000000000312

66. Invernizzi A, Agarwal A, Mapelli C, Nguyen QD, Staurenghi G, Viola F. LONGITUDINAL FOLLOW-UP OF CHOROIDAL GRANULOMAS USING ENHANCED DEPTH IMAGING OPTICAL COHERENCE TOMOGRAPHY. *Retina*. 2017;37(1):144-153.

67. Nakayama M, Keino H, Okada AA, et al. ENHANCED DEPTH IMAGING OPTICAL COHERENCE TOMOGRAPHY OF THE CHOROID IN VOGT–KOYANAGI–HARADA DISEASE. *Retina*. 2012;32(10):2061-2069. doi:10.1097/iae.0b013e318256205a

68. Mehta H, Sim DA, Keane PA, et al. Structural changes of the choroid in sarcoid- and tuberculosis-related granulomatous uveitis. *Eye* . 2015;29(8):1060-1068.

69. Tian M, Tappeiner C, Zinkernagel MS, Huf W, Wolf S, Munk MR. Evaluation of vascular changes in intermediate uveitis and retinal vasculitis using swept-source wide-field optical coherence tomography angiography. *Br J Ophthalmol*. 2019;103(9):1289-1295.

70. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness after treatment of Vogt-Koyanagi-Harada disease. *Retina*. 2011;31(3):510-517.

71. Agrawal R, Li LKH, Nakhate V, Khandelwal N, Mahendradas P. Choroidal Vascularity Index

in Vogt-Koyanagi-Harada Disease: An EDI-OCT Derived Tool for Monitoring Disease Progression. *Transl Vis Sci Technol*. 2016;5(4):7.

72. Dastiridou AI, Bousquet E, Kuehlewein L, et al. Choroidal Imaging with Swept-Source Optical Coherence Tomography in Patients with Birdshot Chorioretinopathy: Choroidal Reflectivity and Thickness. *Ophthalmology*. 2017;124(8):1186-1195.

73. Pichi F, Sarraf D, Arepalli S, et al. The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. *Prog Retin Eye Res*. 2017;59:178-201.

74. Herbort CP Jr, Tugal-Tutkun I, Mantovani A, Neri P, Khairallah M, Papasavvas I. Advances and potential new developments in imaging techniques for posterior uveitis Part 2: invasive imaging methods. *Eye* . 2021;35(1):52-73.

75. Cho H, Pillai P, Nicholson L, Sobrin L. Inflammatory Papillitis in Uveitis: Response to Treatment and Use of Optic Nerve Optical Coherence Tomography for Monitoring. *Ocul Immunol Inflamm*. 2016;24(2):194-206.

76. Zarei M, Abdollahi A, Darabeigi S, et al. An investigation on optic nerve head involvement in Fuchs uveitis syndrome using optical coherence tomography and fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(12):2421-2427.

77. Moore DB, Jaffe GJ, Asrani S. Retinal nerve fiber layer thickness measurements: uveitis, a major confounding factor. *Ophthalmology*. 2015;122(3):511-517.

78. Bellocq D, Maucort-Boulch D, Kodjikian L, Denis P. Correlation in retinal nerve fibre layer thickness in uveitis and healthy eyes using scanning laser polarimetry and optical coherence tomography. *Br J Ophthalmol*. Published online 2016:bjophthalmol - 2016. doi:10.1136/bjophthalmol-2016-308539

79. Ueno S, Kawano K, Ito Y, et al. NEAR-INFRARED REFLECTANCE IMAGING IN EYES WITH ACUTE ZONAL OCCULT OUTER RETINOPATHY. *Retina*. 2015;35(8):1521-1530.

80. Spaide RF. Fundus autofluorescence and age-related macular degeneration. *Ophthalmology*. 2003;110(2):392-399.

81. Durrani K, Foster CS. Fundus autofluorescence imaging in posterior uveitis. *Semin Ophthalmol*. 2012;27(5-6):228-235.

82. Tugal-Tutkun I, Herbort CP Jr, Mantovani A, Neri P, Khairallah M. Advances and potential new developments in imaging techniques for posterior uveitis. Part 1: noninvasive imaging methods. *Eye* . 2021;35(1):33-51.

83. Haen SP, Spaide RF. Fundus autofluorescence in multifocal choroiditis and panuveitis. *Am J Ophthalmol*. 2008;145(5):847-853.

84. Koizumi H, Pozzoni MC, Spaide RF. Fundus autofluorescence in birdshot chorioretinopathy. *Ophthalmology*. 2008;115(5):e15-e20.

85. Hashimoto H, Kishi S. Ultra-Wide-Field Fundus Autofluorescence in Multiple Evanescent White Dot Syndrome. *Am J Ophthalmol*. 2015;159(4):698-706.e1. doi:10.1016/j.ajo.2015.01.015

86. Jack LS, Agarwal A, Sepah YJ, Nguyen QD. Spatial agreement between Goldmann visual field defects and fundus autofluorescence in patients with birdshot chorioretinopathy. *J Ophthalmic Inflamm Infect*. 2016;6(1):18.

87. Boudreault KA, Schuerch K, Zhao J, et al. Quantitative Autofluorescence Intensities in Acute Zonal Occult Outer Retinopathy vs Healthy Eyes. *JAMA Ophthalmol*. 2017;135(12):1330-1338.

88. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. *Circulation*. 1961;24:82-86.

89. Agrawal RV, Biswas J, Gunasekaran D. Indocyanine green angiography in posterior uveitis. *Indian J Ophthalmol*. 2013;61(4):148-159.

90. Herbort CP. Fluorescein and indocyanine green angiography for uveitis. *Middle East Afr J Ophthalmol*. 2009;16(4):168-187.

91. Pichi F, Sarraf D, Morara M, Mazumdar S, Neri P, Gupta V. Pearls and pitfalls of optical coherence tomography angiography in the multimodal evaluation of uveitis. *J Ophthalmic Inflamm Infect*. 2017;7(1):20.

92. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. *Prog Retin Eye Res*. 2018;64:1-55.

93. Kashani AH, Chen C-L, Gahm JK, et al. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. *Prog Retin Eye Res*. 2017;60:66-100.

94. Waizel M, Todorova MG, Terrada C, LeHoang P, Massamba N, Bodaghi B. Superficial and deep retinal foveal avascular zone OCTA findings of non-infectious anterior and posterior uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(10):1977-1984.

95. Tan ACS, Tan GS, Denniston AK, et al. An overview of the clinical applications of optical coherence tomography angiography. *Eye* . 2018;32(2):262-286.

96. Shahlaee A, Pefkianaki M, Hsu J, Ho AC. Measurement of Foveal Avascular Zone Dimensions and its Reliability in Healthy Eyes Using Optical Coherence Tomography Angiography. *Am J Ophthalmol*. 2016;161:50-55.e1.

97. Kim AY, Rodger DC, Shahidzadeh A, et al. Quantifying Retinal Microvascular Changes in Uveitis Using Spectral-Domain Optical Coherence Tomography Angiography. *Am J Ophthalmol*. 2016;171:101-112.

98. Khairallah M. Are the Standardization of the Uveitis Nomenclature (SUN) Working Group criteria for codifying the site of inflammation appropriate for all uveitis problems? Limitations of the SUN Working Group classification. *Ocul Immunol Inflamm*. 2010;18(1):2-4.

99. Stolk-Vos AC, Kasigar H, Nijmeijer KJ, et al. Outcomes in patients with chronic uveitis: which factors matter to patients? A qualitative study. *BMC Ophthalmol*. 2020;20(1):125.

100. Sheppard J, Joshi A, Betts KA, et al. Effect of Adalimumab on Visual Functioning in Patients With Noninfectious Intermediate Uveitis, Posterior Uveitis, and Panuveitis in the VISUAL-1 and VISUAL-2 Trials. *JAMA Ophthalmol*. 2017;135(6):511-518.

101. Pato E, Martin-Martinez MA, Castelló A, et al. Development of an activity disease score in patients with uveitis (UVEDAI). *Rheumatol Int*. 2017;37(4):647-656.

102. Braithwaite T, Calvert M, Gray A, Pesudovs K, Denniston AK. The use of patient-reported outcome research in modern ophthalmology: impact on clinical trials and routine clinical practice. *Patient Relat Outcome Meas*. 2019;10:9-24.