Review Article

Novel diagnostic imaging techniques and applications in anterior uveitis, intermediate uveitis, and scleritis

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Abstract: Uveitis can cause significant visual morbidity and often affects younger adults of working age. Anterior uveitis, or inflammation limited to the anterior chamber (AC), iris, and/or ciliary body comprises the majority of uveitis cases. Current clinical biomarkers and conventional grading scales for intraocular inflammation are mostly subjective and have only a moderate degree of interobserver reliability, and as such they have significant limitations when used in either clinical practice or research related to uveitis. In recent years, novel imaging techniques and applications have emerged that can supplement exam findings to detect subclinical disease, monitor quantitative biomarkers of disease progression or treatment effect, and provide overall a more nuanced understanding of disease entities. The first part of this review discusses automated algorithms for optical coherence tomography (OCT) image processing and analysis as a means to assess and describe intraocular inflammation with higher resolution than that afforded by conventional AC and vitreous cell ordinal grading scales. The second half of the review focuses on anterior segment OCT and OCT angiography (OCTA) in scleritis and iritis, especially with regards to their ability to directly image and characterize the pathologic structures and vasculature underlying these diseases. Finally, we briefly review experimental animal research with promising but more distant human clinical applications, including in vivo molecular microscopy of inflammatory markers and investigation of gold nanoparticles as a potential contrast agent in OCT imaging. Imaging modalities are discussed in the broader context of trends within the field of uveitis towards greater objectivity and quantifiable outcome measures and biomarkers.

Keywords: Uveitis; scleritis; ophthalmological diagnostic techniques

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Introduction

Uveitis encompasses a broad set of ocular inflammatory conditions that often affects working-age adults and contributes to significant visual impairment. Extrapolating from large epidemiological studies, there are over 150,000 new cases per year in the US, and historical data suggests that up to one-third of patients suffer from lasting blindness or vision loss (1,2). Clinically, uveitis is classified in part based on the primary anatomic site of inflammation: anterior (anterior chamber), intermediate (vitreous), posterior (retina or choroid), or panuveitis (all three locations) (3). Anterior uveitis comprises the majority, or an estimated 60–70%, of all uveitis cases and includes such entities as HLA-B27 associated uveitis, uveitis secondary to seronegative spondyloarthropathies, Fuchs' heterochromic uveitis (FHU) and idiopathic uveitis (1,4). A wide array of imaging technologies can aid in the diagnosis and management of uveitic disease—including slit lamp and fundus photography, fluorescein (FA) and indocyanine green angiography (ICGA), optical coherence tomography (OCT),

and OCT angiography (OCTA)—but in both clinical and research settings these techniques are more often leveraged for posterior, rather than anterior or intermediate, disease.

This review will discuss novel imaging technologies such as OCTA, as well as new and emerging applications of conventional imaging modalities, as they pertain to anterior and intermediate uveitis. Scleritis, or inflammation of the outer eye wall, is often grouped with uveitis despite falling outside of its technical bounds and will be considered here as well. In particular, we will contextualize these novel imaging techniques within the broader trend in uveitis towards quantification and establishment of objective clinical measures. Expanding upon the ordinal grading scales for intraocular inflammation established by the Standardization of Uveitis Nomenclature (SUN) working group (3), these new imaging algorithms and indices for intraocular inflammation can more fully describe disease severity and progress in the clinical setting and provide greater sensitivity and resolution for data analysis in research studies.

New methods for assessing intraocular inflammation

Anterior segment OCT assessment of anterior chamber (AC) inflammation

While anterior segment OCT (AS-OCT) itself is a fairly conventional means of evaluating the cornea and AC structures, several studies have described the novel approach of quantifying AC cells and inflammation using this modality. Agarwal *et al.* reported in 2009 a correlation between AC cell counts on time-domain AS-OCT images and the clinical grade of AC cells on examination (5). They described an automated method using MATLAB software whereby images were pre-processed to remove background noise, converted from grayscale to binary black-and-white pixels using a threshold luminance value, and then segmented for hyperreflective spots which were labeled and counted. This algorithm demonstrated the ability to detect cells even in eyes with corneal edema through which no view was possible on exam. Automated results were validated by comparing to manual counts of AC cells in the same images.

Li *et al.* then followed up with a more detailed investigation of automated AS-OCT cell counting by comparing the technique in granulomatous versus non-granulomatous inflammation, as well as in active, quiescent, and healthy normal patients (6). Corroborating prior reports, the authors found strong correlation between automated particle counts and clinical AC cell grades for both granulomatous and non-granulomatous inflammation, with higher absolute counts in non-granulomatous eyes (which they attributed to differences in immune cell composition). Interestingly, this study also identified a subset of clinically quiescent uveitic patients who had a considerable number of AC particles on AS-OCT imaging predominantly in the inferior portion of the chamber. The authors hypothesized that the images are likely identifying large dependent inflammatory cells and debris that are not detected by clinical exam focused on the central regions of the AC.

Further work by Sharma *et al.* reproduced many of the findings previously discussed using a more advanced spectral-domain OCT system with faster scan times and higher axial resolution (7). Their report details volumetric assessment of the degree of AC inflammation by imaging a larger volume of the AC with a higher density of scans, resulting in the identification of significantly greater numbers of particles in their images. Notably the 5 μm axial resolution of spectral-domain OCT means that images are able to capture individual inflammatory cells, which range in size from 10–20 microns (5), whereas previous time-domain systems with poorer resolution were likely only able to delineate clumps of cells in aggregate. Additionally the volumetric assessment allows for analysis of total cell counts in the AC rather than individual line scans, presumably giving a more accurate assessment of the degree of inflammation in the AC.

More recently, studies of AC inflammation on a state-of-the-art swept-source OCT platform were able to quantify AC flare, in addition to AC cells, which was previously not possible except in very extreme cases of fibrinous AC reaction (5,8). Invernizzi *et al.* compared image brightness values within a region of the AC to the brightness of air outside of the eye in the same image. This comparison yielded an "aqueous-to-air relative intensity (ARI) index" that could be used as an objective surrogate marker for aqueous flare with good inter-observer reliability (78%) and correlation to results measured by antiquated and cumbersome gold-standard laser flare photometry (LFP) (8). The authors identify several shortcomings of this new index for aqueous flare, namely the need to collect brightness values and perform calculations manually, low correlation with LFP results at low levels of flare, and the influence of central corneal thickness of ARI index measurements.

Nevertheless, their findings are significant for quantifying an aspect of intraocular inflammation that in clinical practice to date has been largely assessed qualitatively and subjectively.

Taken together, the work to develop a quantitative, OCT-based method for measuring AC inflammation promises several advantages over current practices in the diagnosis and management of anterior uveitis. First, automated imaging algorithms likely have higher sensitivity for detecting AC cell than clinician exams and are better able to penetrate through corneal opacities, thereby providing a more nuanced and potentially more accurate picture of the patient's level of inflammation. Second, quantitative OCT assessment measures of AC cell and flare potentially would provide more objective and reliable measures of inflammation than those described within the current SUN working group framework. For clinical grading of AC cell, exact inter-rater agreement is fairly low (less than 50%) (9), and for aqueous flare grading is largely descriptive ("faint", "moderate", "marked", and "intense") (3). Thus OCT image-based numerical counts and indices may be more useful as disease biomarkers for patients being seen over multiple clinic visits, or by different clinicians. Lastly, the continuous, numerical nature of AC cell counts and the ARI index for aqueous flare vastly expands the range of possible disease states as compared to the five, non-linear levels of disease severity described under the SUN grading criteria. If implemented in future research contexts, these quantifiable outcome measures would have the potential for more precise delineation of treatment efficacy and effect size.

OCT quantification of inflammation in the vitreous

In parallel with the work done on quantifying AC cell and flare, Keane *et al.* have outlined a method for quantifying inflammatory activity in the vitreous by way of measuring its signal intensity on OCT scans. Similar to the image processing workflow for AS-OCT images in AC cell counting, here scans encompassing the macula and vitreous cavity are segmented either manually or automatically, binarized into light and dark pixels according to a threshold intensity, and then analyzed for mean pixel or signal intensity in the vitreous space and in the retinal pigment epithelium (RPE) layer. This allows for calculation of an optical density ratio—the "VIT[vitreous]/RPE-relative intensity"—comparing mean OCT pixel intensity within the vitreous cavity to that of the RPE, which serves as an internal control and reference standard (10,11).

Comparison of the VIT/RPE-relative intensity against conventional measures of disease activity validate its utility as a quantitative marker of vitritis. At the most basic level, the VIT/RPE-relative intensity is preferentially elevated in uveitic eyes with clinically active vitritis and is able to distinguish these eyes from both normal controls as well as uveitic eyes without vitritis. It also correlates significantly with visual acuity, clinical vitreous haze grading using the National Eye Institute (NEI) standardized images, and even AC cell and flare (10,12). Inter-rater reliability was high, indicating that the measurement and calculation of VIT/RPE-relative intensity is highly reproducible. Subsequent work by the same group further refines the quantification of vitreous inflammation by implementing automated image segmentation that improves the speed of image analysis by an order of magnitude to seconds rather than minutes per patient. Additionally they outline a second image characteristic—that of "textural intensity"—which complements the mean signal intensity as a quantifiable descriptor of vitritis (11). This textural intensity index mathematically describes the heterogeneity and variation of pixel intensities, essentially the degree of "graininess", within the vitreous image and correlates even more strongly to clinical vitreous haze scores than does the VIT/RPE relative signal intensity measure.

More recent studies have further upheld the validity of the VIT/RPE-relative intensity ratio as an objective measure of vitritis. A large observational cohort study of 105 eyes showed that results are reproducible, although not necessarily directly comparable, between Zeiss and Heidelberg OCT platforms, and values remain comparable and unaltered by lens status or prior vitrectomy (13). The latter finding is particularly salient given the high incidence of both cataract surgery and vitrectomy in active uveitis patients and supports the utility of the VIT/RPE-relative intensity ratio as a useful clinical marker in real-world settings. Even more promising, an investigation by Sreekantam *et al.* showed that the VIT/RPE-relative intensity measures are reduced after steroid treatment in conjunction with other established disease biomarkers such as central macular thickness (CMT) measurements on OCT and best-correct visual acuity (14).

A few limitations remain to be worked out in the clinical and research implementation of this novel quantitative variable for vitritis. Montesano *et al.*, in testing OCT-based quantitative vitritis grading in "real-world conditions", identified focus and image positioning issues as potential sources of instrument bias (15). They found that improper

image focus, especially if displaced anteriorly, could significantly and artifactually elevate the VIT/RPE-relative intensity measurements and produce falsely elevated interpretations of vitritis severity. Similarly, inferior displacement of the retina slab within the acquisition window also increased measured values, which presents a potential practical challenge as retinal thickening and cystoid macular edema, both commonly seen in uveitis, can often force the retinal OCT image to be inferiorly displaced. Nevertheless, the use of OCT-derived quantitative measures of vitritis severity represents a notable advancement over current, relatively subjective descriptors for vitreous cell and haze. It brings with it many of the same advantages that automated AC cell counting algorithms pose for AC inflammation, namely improved inter-rater reliability and expanded descriptive capabilities and range.

Novel imaging approaches for episcleritis and scleritis

Like the groundbreaking work in uveitis by the SUN working group, Sen *et al.*'s series of reference images and standardization of grading criteria constructs an important framework for the discussion and diagnosis of scleritis. Mirroring the five-point scale used to describe intraocular inflammation, scleritis severity was assessed on the basis of residual injection after instillation of 10% phenylephrine to the eye, ranging from complete blanching to severe diffuse redness and scleral thinning with necrosis (16). However as previously discussed, the use of reference images and ordinal grading scales also carries with it a degree of examiner subjectivity as well as descriptive limitations. Since the publication of Sen's landmark paper in 2011, the widespread adoption of AS-OCT and the emergence of OCTA for anterior segment structures offer several novel and more objective diagnostic approaches to scleritis.

Levison *et al.* examined OCT images for 28 patients with scleritis and described the presence of superficial hyporeflective lesions corresponding to nodules and deep hyporeflective cavities within the sclera corresponding to dilated blood vessels. They note that the amount of hyporeflective spaces appeared to loosely correlate with degree of conjunctival injection but that within each scleritis grade, and especially at higher grades of severity, OCT manifestations varied considerably. A number of patients were followed longitudinally and imaged before and after treatment; in these patients, resolution of hyporeflective nodular lesions and vascular dilation within the sclera was found to correlate with clinical improvement and stepwise improvement in scleritis grade (17). Additional OCT imaging studies examine potential quantifiable measures of disease severity by comparing scleral thickness in scleritis, episcleritis, and healthy normal patients. They found that patients with scleritis generally had deeper involvement of intrascleral edema and vascular congestion, and overall greater scleral thickness measurements as compared to episcleritis patients and healthy controls. These studies conversely found that vascular congestion and dilation in episcleritis is generally superficial and associated with less scleral thickening (18,19). Thus, AS-OCT provides objective information, both qualitative and quantitative, that can corroborate clinical observations and aid in diagnosis, decision-making, and evaluating treatment response (20).

OCTA is a novel imaging modality that detects areas of differences, or decorrelation, within repeated scans of a tissue over time and interprets those areas as blood flow within vasculature (21). The advent of OCTA for limbal, conjunctival, and scleral vasculature allows for more in-depth examination of the intrascleral and vascular changes in scleritis seen on AS-OCT. Akagi *et al.* demonstrated that in normal patients, OCTA compares favorably to scleral and aqueous FA and ICGA in terms of resolution, without the need for invasive administration of intravenous dye agents. Moreover, OCTA can scan to depths of 1 mm and provide spatial resolution rather than flat two-dimensional angiography images; the resulting images can then be post-processed and analyzed for vessel density and diameter at different layers of the eye wall (22,23). In looking specifically at OCTA for scleritis and episcleritis, Hau *et al.* segmented the eye wall into three layers: the superficial conjunctival epithelium, the conjunctiva-episclera complex, and the deep episclera-sclera complex. They found that the vessel density index (VDI) was significantly elevated in all three layers for both episcleritis and scleritis as compared to normal controls, and that there was significantly greater thickening of the deeper episclera-sclera layer in scleritis as compared to episcleritis (24). This preliminary data suggests that there may be quantitative markers that can be derived from OCTA images that differentiate scleritis from episcleritis from normal subjects. However, much work remains to be done with regards to validating these measures against clinical scleritis grades, pain scores, and

treatment effects.

Novel and uncommon iris imaging techniques in the evaluation of anterior uveitis

As one of the most visible structures in the AC, the iris can provide a wealth of information on clinical exam in the evaluation of anterior uveitis, including its shape and conformation, presence of synechiae, patterns of atrophy, constriction or dilation, and neovascularization. Likewise, many of these changes can be captured through various imaging modalities. Basarir *et al.* described the use of AS-OCT to assess AC anatomy and iris thickness and bowing in patients with unilateral FHU. They report that relative to the normal fellow eye, eyes with FHU had deeper AC s and thinned and back-bowed irides (25). The authors hypothesize that these anatomic alterations collectively stem from the primary problems of iris atrophy and atony seen commonly in FHU. Liu *et al.* conducted a complementary study of the iris in FHU using near-infrared autofluorescence (AF). They found that in healthy subjects, AF intensity concentrated in areas of pigmentation including the pigment ruff at the pupillary border and the collarette in the mid-periphery. In eyes with age-related atrophy or non-FHU types of uveitis, AF signal was fairly uniformly depleted, but in eyes with FHU, AF attenuation was distinctively patchy and almost "petaloid" in appearance (26). Liu posits that adjunctive imaging studies of the iris in FHU can detect subclinical disease and/or help distinguish FHU from other uveitis entities that might require more aggressive treatment. In short, iris imaging may help clarify a confounding clinical picture and reduce the often years-long delay in diagnosis of FHU (27).

Iris vasculature is also known to dilate in the setting of anterior uveitis more generally and thus represents an interesting target for studies using OCTA (28). Pichi *et al.* conducted a study using OCTA to examine the iris vasculature of 35 patients with anterior uveitis. The vascular flow rate was estimated from the brightness level within the imaged iris blood vessels, and the degree of vessel dilation was measured using the vascular volumes in post-processed scans. Both parameters were found to correlate with the degree of AC cell on exam (29). At the same time, OCTA of the iris currently suffers from a few tissue-specific limitations. First, the iris vasculature is affected by pupil dilation and size, which in turn affects the reproducibility of data across different patients, examiners, and environmental conditions. Second, OCTA tissue penetration in the iris is partly dependent on iris pigmentation levels, which further impacts the ability to compare quantitative results among different patients and populations. Yet despite these early shortcomings, the adaptation of OCTA for iris vasculature potentially offers a way to assess and quantify a facet of anterior segment inflammation that has until now been largely overlooked.

Other imaging considerations in anterior uveitis

One area of the eye that has so far been largely overlooked in this discussion of imaging for anterior and intermediate uveitis is, understandably, the retina and choroid. Yet with rapid improvements and advances in imaging modalities for the posterior segment, recent studies now suggest that intermediate, and even anterior, uveitis can manifest subtly in the retina and choroid as well. Kim *et al.* used OCTA to explore the impact of uveitis on retinal capillary density and morphology. While the majority of uveitic patients included in this series had posterior uveitis, one-sixth of the subjects had various forms of anterior uveitis without macular edema, and even in these patients the retinal microvascular density and branching patterns were noted to be thinned (30). An unrelated study using enhanced depth imaging (EDI)-OCT of the choroid in 16 patients with unilateral HLA-B27 anterior uveitis similarly found significant choroidal thickening in the acutely affected eye compared to unaffected fellow eye, without significant concomitant differences in CMT. The increase in subfoveal choroidal thickening then resolved after resolution of the acute anterior uveitic period (31). Finally, Wintergerst *et al.* compared OCTA retinal vasculature parameters for intermediate uveitis patients to age-matched controls and found that all parameters—including vessel density, vessel diameter index, and fractal (branching) dimension—were decreased in the superficial and deep retinal layers of eyes with anterior uveitis. This reduction mostly persisted even for the subset of patients who did not have cystoid macular edema (32). Together, the data imply, perhaps counterintuitively, that disease activity in anterior and intermediate uveitis can be observed in the subtle remodeling of the retina and choroid, even in the absence of macular edema.

Beyond the many readily available imaging modalities discussed in this review are several experimental molecular imaging techniques currently being investigated only in small animal models that might one day have clinical relevance for patients. One such approach described by Xie *et al.* involves the use of microspheres (particles between

1 μm and 1 mm in size) conjugated with a glycoprotein ligand that recognizes and binds sites of vascular endothelial injury. In a mouse model of endotoxin-induced uveitis injected with fluorescent microspheres, *in vivo* microscopy of the iris was able to localize sites of inflammatory injury and monitor disease course and treatment efficacy (33). A second molecular imaging approach involves using gold nanoparticles as a possible OCT contrast agent, which would potentially make possible many exciting diagnostic and therapeutic applications, although this approach currently faces regulatory hurdles (34). In the end, any novel imaging technique would face important questions of cost, efficiency, and invasiveness and would have to demonstrate a diagnostic or therapeutic capability not already fulfilled by existing modalities and applications.

Conclusions

As our understanding of uveitis expands, so too will our need for more tailored therapies and, with it, more nuanced diagnostic and imaging capabilities. New imaging modalities like OCTA, and novel applications such as automated OCT algorithms for AC cell counting and vitritis quantification, help support this trend towards greater objectivity and inter-observer reliability. Ultimately, imaging in uveitis can serve as the basis for more precise descriptions of disease severity, more accurate assessments of prognosis, and more sophisticated understanding of treatment effects.

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