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Structural Endpoints and Outcome Measures in Uveitis

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Keywords
Endpoint · Outcome · Outcome measure · Biomarker · Imaging biomarker · Instrument-based measure · Uveitis · Inflammatory eye diseases

Abstract
Most uveitis entities are rare diseases but, taken together, are responsible for 5–10% of worldwide visual impairment which largely affects persons of working age. As with many rare diseases, there is a lack of high-level evidence regarding its clinical management, partly due to a dearth of reliable and objective quantitative endpoints for clinical trials. This review provides an overview of available structural outcome measures for uveitis disease activity and damage in an anatomical order from the anterior to the posterior segment of the eye. While there is a multitude of available structural outcome measures, not all might qualify as endpoints for clinical uveitis trials, and thorough testing of applicability is warranted. Furthermore, a consensus on endpoint definition, standardization, and "core outcomes" is required. As stipulated by regulatory agencies, endpoints should be precisely defined, clinically important, internally consistent, reliable, responsive to treatment, and relevant for the respective subtype of uveitis. Out of all modalities used for assessment of the reviewed structural outcome measures, optical coherence tomography, color fundus photography, fundus autofluorescence, and fluorescein/indocyanine green angiography represent current "core modalities" for reliable and objective quantification of uveitis outcome measures, based on their practical availability and the evidence provided so far.

Introduction

Most uveitis entities are rare diseases but, taken together, are responsible for 5–10% of worldwide visual impairment which largely affects individuals of working age [1–4]. As with many rare diseases, there is a dearth of

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evidence regarding its clinical management [3, 4]. Prerequisites for high-level evidence around disease outcome and therapeutic efficacy are reliable and objective quantitative endpoints, which are necessary, for example, in randomized controlled clinical trials. Currently, we largely lack such endpoints for uveitis, as disease activity is primarily evaluated on clinical examination using subjective gradings with poor reliability [4–7]. This negatively impacts the implementation of randomized controlled clinical trials and generation of high-level evidence.

Historically, only clinical evaluation was available for uveitis assessment and intraocular inflammation ratings [8, 9], and it has been the reference standard for many years. The Standardization of Uveitis Nomenclature (SUN) initiative undertook a critical rationalization of a number of key metrics. However, in general terms, clinical examination assessments have the limitations of being subjective, frequently have relatively poor agreement between different clinicians, and are relatively imprecise (being qualitative or semiquantitative ratings) [4–7].

In contrast, instrument-based outcome measures offer objective measures which are potentially more reliable and more precise, being quantifiable alternatives for the assessment of various ocular endpoints including intraocular inflammation and thus uveitis activity. Ophthalmic imaging emerged in the late 1920s with the first available color fundus photography devices [10], and capabilities expanded with the development of fluorescein angiography in the 1960s [11] and indocyanine green angiography in the 1970s [12]. With the advent of technological advancement over the last few decades, many additional imaging modalities have been developed and implemented in routine clinical practice, which allows for a multimodal approach to disease evaluation and a variety of available structural outcome measures.

However, these numerous available different endpoints considerably increase heterogeneity in outcomes, which limits comparability of trials and hampers development of clinical practice guidelines [4]. To further facilitate a consensus on endpoints used for uveitis, an overview on available structural outcome measures is warranted.

When employing outcome measures, it is helpful to clearly stratify for measures of current disease *activity* (hence of a reversible nature) and of disease complications or permanent structural changes representing *damage* (of an irreversible nature). Against this background, we will review available structural outcome measures for uveitis disease activity and damage in an anatomical order from the anterior to the posterior segment of the eye, including those with proven or potential use as outcome measures.

Methods

MEDLINE was searched using truncations and abbreviations of the following terms with no time restrictions: uveitis, Birdshot, choroiditis, Koyanagi, placoid pigment, acute retinal necrosis, progressive outer retinal necrosis, punctate inner, pigment epitheliopathy, white dot, vitritis, acute zonal occult, retinitis, vasculitis, sarcoidosis, Behçet, behcet, inflammatory eye disease, endpoint, outcome, measure, biomarker, quantitative, instrument, automated, algorithm, and computer. Only literature with English abstracts was included. No meta-analysis on outcome measure validity and reliability was performed, as this was beyond the scope of this narrative review. Any sequel of scleritis or of secondary glaucoma due to uveitis in terms of measures of disease damage (e.g., retinal nerve/ganglion cell layer damage) were excluded.

Anterior Segment

Anterior Chamber Cells

One of the most common signs of inflammatory activity in uveitis are anterior chamber cells. Various semiquantitative classification systems for clinical grading have been described, and the most common and established one was introduced by Hogan et al. [8], encompassing "1+" to "4+," and later adapted by the SUN Workshop of 2005 to add an additional "0.5+" class [13]. Optical coherence tomography (OCT, Fig. 1) and laser flare-cell photometry have been proposed for objective grading of anterior chamber cells. While both offer an objective and potentially automated quantification and have a high correlation with the clinical grading, OCT is likely to become the dominant technique for anterior chamber cell quantification, as it is well established and offers a higher data volume [14–16]. Recently, it has been suggested to differentiate the anterior chamber cell population using spectroscopic OCT, which could allow stratification of different leucocyte cell populations [17].

Anterior Chamber Flare

Anterior chamber flare grading for assessment of disease activity is variable in use, as it is influenced by many factors, for example, lens status and drug-induced mydriasis, yet it constitutes an essential part of clinical evaluation [8, 18]. Similar to anterior chamber cell grading, the currently established clinical anterior chamber flare grading was already introduced in the 1950s by Hogan and colleagues [8] and classifies flare from "1+" to "4+" based on visibility of iris details on slit-lamp examination. A variety of instruments has been proposed for objective anterior chamber flare assessment, with noninvasive laser flare photometry being the most validated technique, showing a moderate to strong correlation with the clinical SUN classification grading, as well as the anterior chamber protein concentration [19]. Additional methods proposed include OCT, ocular flare analysis meter, and double-pass technique (providing combined information on aberration and intraocular scatter) [15, 19–21].

Keratic Precipitates

Keratic precipitates are another measure of disease activity and can be clinically stratified into granulomatous ("mutton fat") and nongranulomatous (and stellate, fine, and pigmented, i.e., old) [8]. Using in vivo confocal microscopy, keratic precipitates can be further stratified, for example, globular, infiltrating, smooth-round-

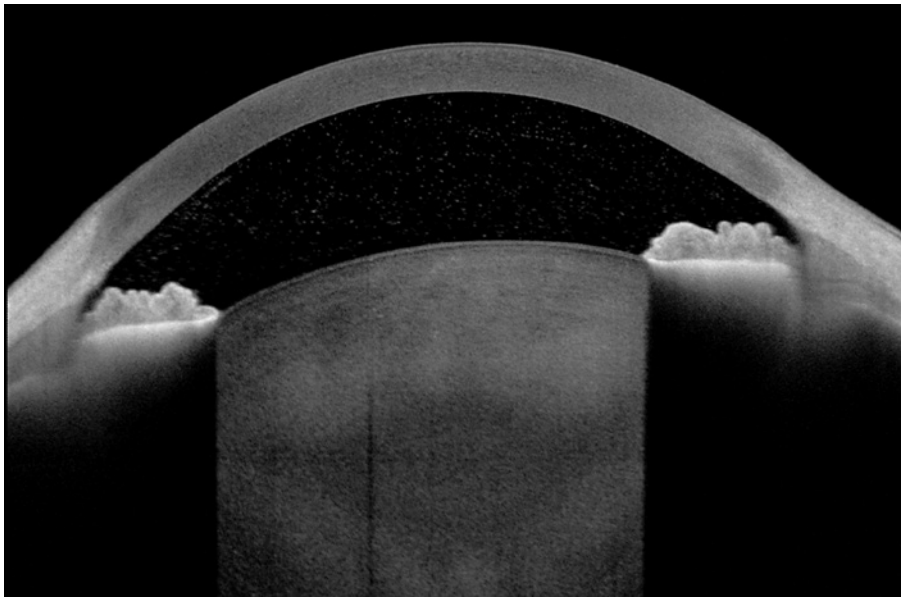

Fig. 1. Anterior chamber cells and flare on swept-source optical coherence tomography in a case of anterior uveitis (ANTERION; Heidelberg Engineering; for better visualization, contrast has been decreased and brightness increased via postprocessing).

ed, stippled, dendritiform, and cruciform, which may aid in differentiating infectious from noninfectious anterior uveitis [15, 22–34]. Keratic precipitates can also be visualized on OCT; however, further research is necessary to determine its clinical relevance [35].

Other Anterior Segment Outcome Measures

Besides anterior chamber cells, flare, and keratic precipitates, endothelial dust, iris nodules, and conjunctival injection are additional possible measures for disease activity which can be graded clinically or on slit-lamp photographs [15]. Conjunctival congestion is classified dependent on extent [8]. There can be additional corneal involvements which are measures of disease activity including corneal dendrites in cases of secondary uveitis in herpes simplex keratitis and interstitial keratitis, for example, in syphilis. Furthermore, there can be secondary findings of disease activity like corneal opacity and Descemet membrane folds in case of increased intraocular pressure. An additional potential measure of disease activity in the anterior segment of the eye are alterations of iris and episcleral perfusion, which can be analyzed by fluorescein, indocyanine green, and indirectly by OCT angiography (OCT-A) [15, 36–38].

Measures of disease damage in anterior uveitis include anterior/posterior synechiae, iris atrophy, iris depigmentation, secondary cataract, and corneal endothelial cell density. Corneal endothelial cell density is reduced in certain anterior uveitis entities including chronic severe inflammation with granulomatous keratic precipitates, Fuchs uveitis, and viral anterior uveitis and can be assessed by corneal endothelial specular microscopy [15, 39]. However, dependent on the available optical resolution, this can be challenging. Anterior segment structural changes like synechiae and iris atrophy can also be assessed on OCT or slit-lamp photography, which can facilitate objective and reliable quantification as well as comparison over time [15, 40].

Vitreous

Vitreous Cells

Vitreous cells, a sign of inflammatory activity, which are thought to be predominantly T lymphocytes in uveitis [41], are clinically assessed as they have been described by Kimura et al. [9], which was later extended to a semiquantitative scale from "1+" to "4+" [42]. Slit-lamp examination and funduscopy allow assessment of anterior and posterior vitreous cells. However, both anterior and posterior vitreous body cell assessment do not take into account the total spatial distribution of inflammatory cells in the vitreous. Although it was agreed that the presence of vitreous cells was an important clinical feature, no consensus could be reached on a standard grading system.

Additionally to floating vitreous body cells seen on clinical examination, hyperreflective preretinal deposits and deposits/consolidations at the posterior surface of the vitreous can be present on OCT in specific uveitis entities (including toxoplasmosis, syphilis, and candida chorioretinitis) [40, 43]. In case of massive deposits, a shadowing effect is generated which is sometimes described as "rain-cloud sign" [40, 43].

Vitreous Haze and Opacities

Vitreous inflammation can be evaluated in a more general and potentially more accurate [42, 44] manner by assessment of vitreous haze and opacities. Initially, evaluation was based on a qualitative 5-step grading of the haze and classification of opacities as fine/coarse/stringy [9]. To try to improve objectivity, Nussenblatt et al. [44] proposed a 6-step scale in which the examiner compared the indirect biomicroscopic view of the fundus against reference images; this was later adapted by the SUN initiative [13], replacing the trace grade with a 0.5. To further improve discrimination and objectivity, Davis and colleagues [45] expanded this to a 9-step scale in which fundus photographs are taken under standard conditions, and these photographs are compared to a reference set of images. Reliability of both pro-

posed scales for clinical vitreous haze grading was moderate with the 9-step scale potentially being more suitable for clinical trials [5, 6, 46]. It is important to bear in mind that correction of vitreous haze grading for any other media opacities, for example, lental or corneal, is essential and that this is a further subjective element that may reduce reliability.

To allow truly objective quantification of vitreous haze, OCT has been proposed for quantification of vitreous haze, and first applications are promising with good reliability and correlation with the clinical grading [47–49]. Furthermore, there are promising first attempts for automated vitreous haze grading on color fundus photography [50]. Further, ultrasound biomicroscopy and vitreous fluorophotometry can provide additional information over clinical examination on vitritis/pars planitis activity [15, 51, 52].

In addition to vitreous cells and haze, inflammatory activity can be assessed by presence of snowballs and/or snowbanks (especially if newly appearing) [9]. Possible disease complications of vitreous inflammation include vitreous detachment and/or retinal breaks [9]. Importantly, all discussed measures only provide a grading of inflammation in a relatively small part of the total vitreous body.

Epiretinal Membrane

One additional possible complication from retinal/vitreous inflammation is the formation of a secondary epiretinal membrane, which can contribute independently to vision loss in uveitic eyes. It can be assessed by funduscopic examination, blue reflectance imaging, multicolor imaging, and OCT, though the latter is thought to be the most sensitive for its identification [53, 54].

Retina and Choroid

Macular Intra-/Subretinal Fluid

Intra- and subretinal fluid is a common sign of inflammation in uveitis (especially in presence of chronic disease [55]) and can have a profound impact on central visual acuity and patient-reported outcome measures such as quality of life [55, 56]. Its diagnosis and evaluation was revolutionized by the advent of OCT, which allows for a reliable assessment and quantification of central retinal changes [57, 58]. Macular fluid can present in uveitis as diffuse and cystoid intraretinal or subretinal fluid, and these subentities may respond differently on treatment [55, 59–61]. Its application as an objective, quantitative endpoint for uveitis is well established and could be used as a blueprint for the development of novel quantitative endpoints [4, 62–80]. A 20% change in retinal thickness in patients with macular edema seems to be optimal for clinically important changes in visual acuity and may therefore be considered as an endpoint for clinical trials [68]. Disorganization of retinal inner layers is a surrogate marker of visual acuity in participants with current or resolved uveitic macular edema [81]. Uveitic macular edema may show morphological characteristics discriminating it from other causes of macular edema [82, 83].

Yet, while OCT has widely become the reference standard for evaluation of macular edema, fluorescein angiography still has additional diagnostic value, as both imaging techniques are complementary investigations revealing potentially different pathophysiologic aspects of macular edema. Fluorescein angiography is more sensitive in detecting very subtle macular leakage which may represent mild edema or leakage in the absence of edema [58, 84–89].

Retinal and Chorioretinal Inflammatory Lesions

Appearance of retinal/choroidal lesions on funduscopic examination and color fundus photography in terms of color, border "fluffiness"/"fuzziness," hemorrhage, prominence, opacity of the lesion, and surrounding retinal edema is a well-known measure of disease activity [9]. Dependent on the specific disease entity, evaluation on various other imaging techniques can provide valuable additional information.

The substructure of retinal/choroidal lesions can be assessed by OCT and frequently reveals hyperreflective aspects [40, 43, 90]. Furthermore, dependent on disease entity and activity, specific retinal layers can be disrupted/thickened/altered in characteristic ways [43, 91, 92]. For example, disruption of the ellipsoid zone in multiple evanescent white dot syndrome (MEWDS) is thought to correspond to swollen photoreceptor bodies [43]. Several diseases are associated with subretinal material, which can be a sign of active inflammation: for example, in Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, vitreoretinal lymphoma (as masquerade syndrome), and subretinal fibrosis [43]. Choriocapillaris hyporeflectivity can be present in primary inflammatory entities of the choriocapillaris and might represent a disease complication [43]. In addition, near-infrared reflectance can be useful in some posterior uveitis entities including white dot syndromes and might indicate impairment of the photoreceptor layer (Fig. 2) [90, 93].

Fundus autofluorescence has emerged as a noninvasive imaging technique that uses the fluorescent properties of intrinsic fluorophores to evaluate the retinal pigment epithelium/photoreceptor complex [94]. Fundus autofluorescence characteristics of retinal/choroidal lesions can be described in terms of hypo-/iso-/hyperautofluorescence and can be used to evaluate inflammatory activity and size and number of inflammatory retinal/choroidal lesions in uveitis (Fig. 2). As appearance of lesions on fundus autofluorescence is likely of prognostic value, it has been suggested for monitoring of retinal/choroidal lesions and can also aid automatic quantification of retinal/choroidal lesions [95–99]. Different fundus autofluorescence modalities might differ in eligibility dependent on excitation wavelengths and concomitant different penetration depths and molecular targets for excitation. Moreover, quantitative autofluorescence may provide additional insights and objective measures [100].

Additional imaging modalities which can provide insightful information for evaluation of retinal/choroidal lesions are fluorescein and indocyanine green angiography. Differentiation of angiographic findings as staining, leakage, blocking, or true capillary dropout can be helpful in stratification of different uveitis entities as well as assessment of intraocular inflammation, but may also pose challenges due to, for example, similarities in angiographic appearances. Fluorescein leakage in the area of retinal/choroidal lesions can indicate disease activity. Dependent on disease entity, hypo-/hyperfluorescence due to staining/pooling/window defects/blocking by retinal/choroidal lesions or in areas of clinically uninvolved fundus during different stages of angiography (early vs. late) and disease can be present [101–103]. Certain retinal pigment epithelium alterations can be visualized by characteristic fluorescein angiography patterns (e.g., "retinal pigment epithelium mottling" in acute posterior multifocal placoid pigment epitheliopathy and serpiginous choroiditis) [101].

Wide-field retinal imaging is a very relevant addition to the current imaging modalities as it allows for the additional visualization of peripheral lesions/ischemia/vasculitis and therefore can alter

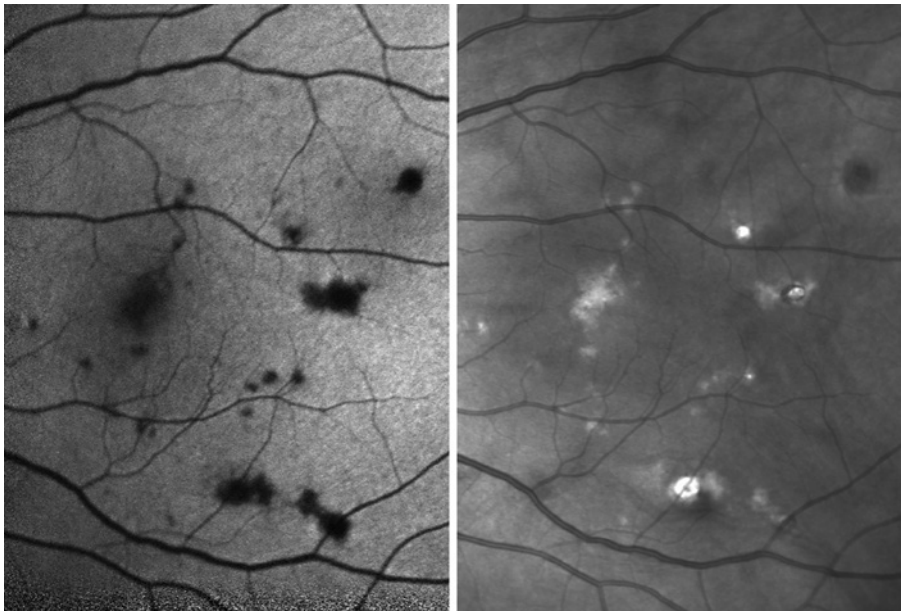

Fig. 2. Chorioretinal lesions in punctuate inner choroidopathy on "blue" fundus autofluorescence (450-nm excitation wavelength, left) and near-infrared reflectance imaging (right; both Spectralis HRA; Heidelberg Engineering).

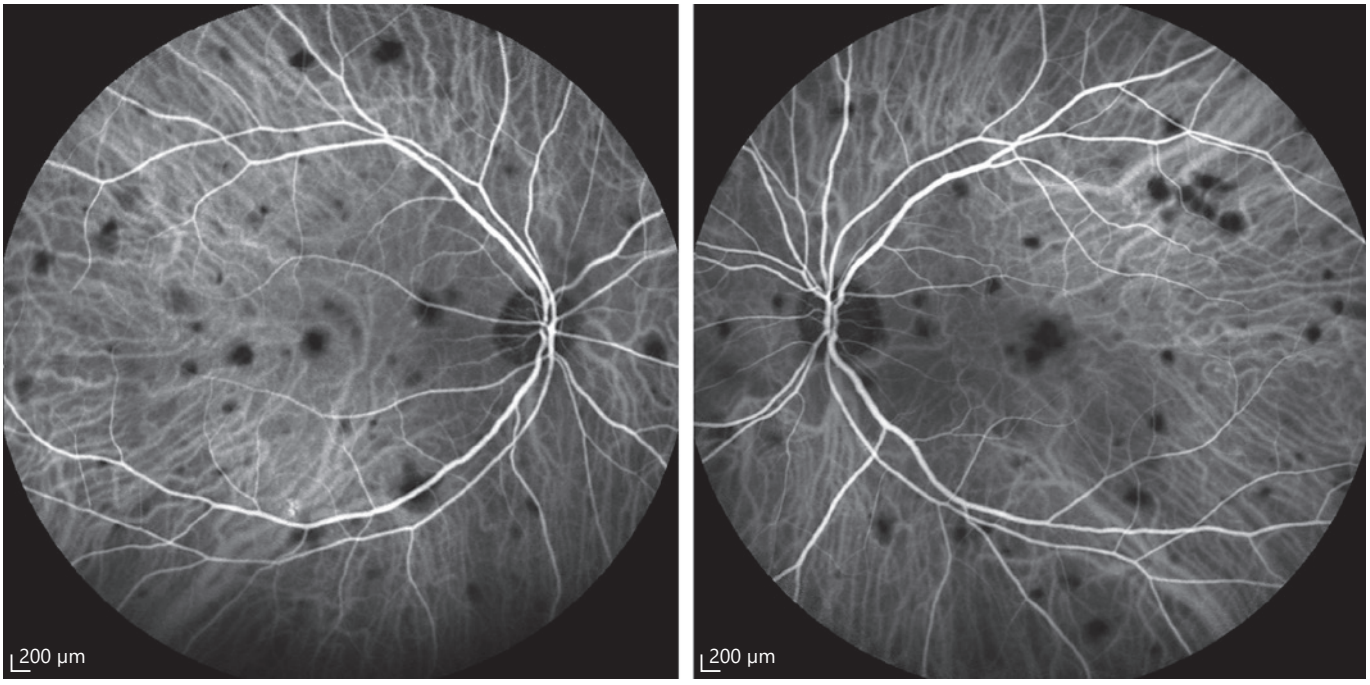

Fig. 3. Bilateral choroidal granulomas on indocyanine green angiography visible as hypofluorescent "dark dots" in a case of birdshot retinochoroidopathy (intermediate phase; Spectralis HRA; Heidelberg Engineering).

management decisions compared to standard-of-care imaging and clinical examination in posterior and intermediate uveitis [104–108]. Adaptive optics imaging might allow identification of additional imaging biomarkers such as irregularities in the reflectivity of the photoreceptor mosaic and stratification of vascular sheathing (see also "*vasculitis*" below), which could serve as endpoints in uveitis trials [109–113]. Although chorioretinal lesions can simply be a sign of acute disease activity with complete resolution, they are commonly associated with scarring and other complications such as ischemia and neovascular or epiretinal membrane formation.

Choroidal Granulomas and Choroidal Thickening/Thinning

Stromal choroidal inflammatory activity in terms of choroidal granulomas as in birdshot retinochoroidopathy, Vogt-Koyanagi-

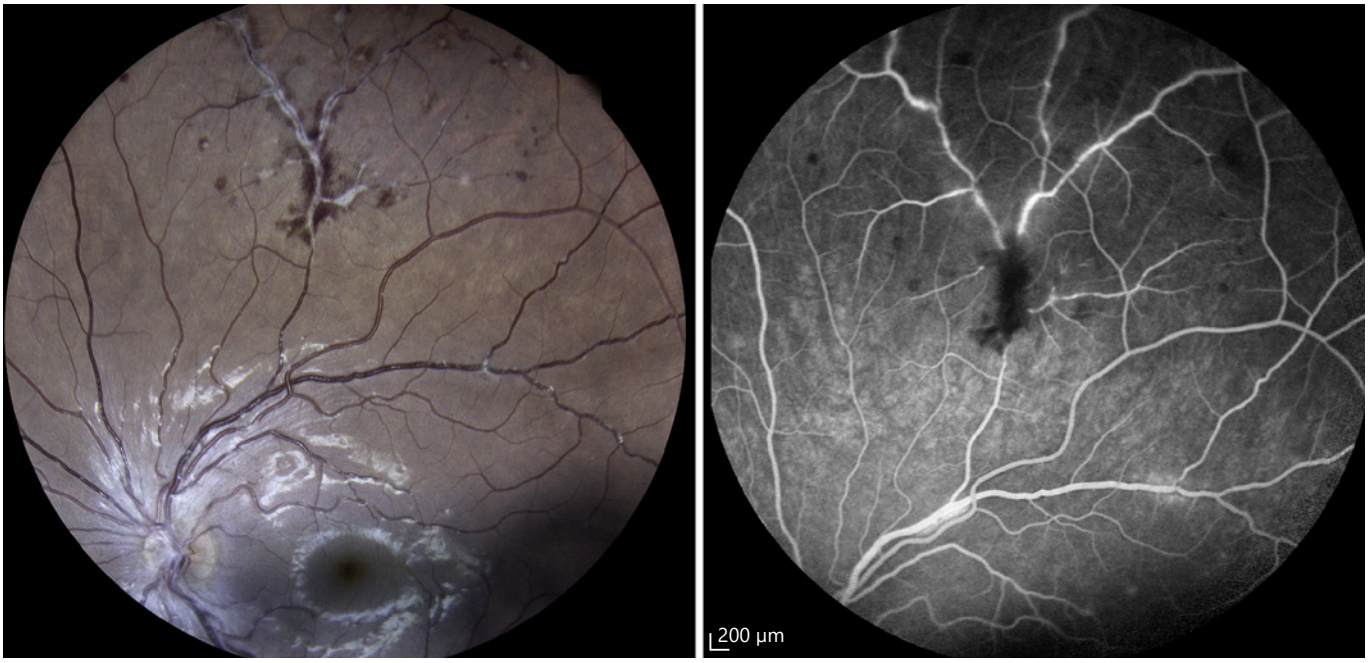

Fig. 4. Vasculitis signs on color fundus photography (left; Eidon; CenterVue) and fluorescein angiography in a case of idiopathic retinal vasculitis (right; late phase; Spectralis HRA; Heidelberg Engineering).

Harada disease, sympathetic ophthalmia, sarcoidosis, and tuberculosis can be assessed using indocyanine green angiography, and a standardized angiographic protocol to increase reliability has been proposed (Fig. 3) [114, 115]. These choroidal granulomas can potentially also be visualized noninvasively on OCT and OCT-A; however, the limited depth resolution should be taken into account [40, 43, 116–118]. Enhanced depth imaging OCT may help to differentiate between etiologies and also to monitor therapy, as it allows improved visualization of choroidal structures [119, 120].

Due to choroidal infiltration by inflammatory cells or granulomas or increased filling of the choroidal vasculature, choroidal thickening can occur, either globally or associated with localized retinal/choroidal lesions [43]. Choroidal thickness varies during different stages of disease, and it can indicate disease activity, for example, Vogt-Koyanagi-Harada disease, acute zonal occult outer retinopathy, and birdshot retinochoroidopathy [121–124]. It can be assessed on enhanced depth spectral-domain and swept-source OCT, with the latter being superior because of a higher signal penetration depth [117, 125]. Besides variations in thickness, choroidal involvement can also be present in terms of small structural and reflectivity changes visible on enhanced depth spectral-domain and swept-source OCT (e.g., hyperreflective dots and diffuse hypo-/hyperreflectivity) [126]. Furthermore, the ratio of luminal and stromal interstitial choroidal area (choroidal vascularity index) can be quantified on OCT and may aid monitoring disease activity [127].

Choriocapillary Nonperfusion

Choriocapillary nonperfusion due to presumed inflammatory lesions (unspecific measure of disease activity)/atrophy (measure of disease damage) in the early phase of fluorescein angiography and in the intermediate and late phase of indocyanine green angiography is typically seen in primary inflammatory entities of the choriocapillaris (e.g., acute posterior multifocal placoid pigment epitheliopathy, MEWDS, and serpiginous choroiditis) [87] and can also be assessed noninvasively using OCT-A (however, masking and projection artifacts need to be taken into account as possible confounders) [38, 40, 128]. These nonperfused areas of choriocapillaris can be associated with funduscopically visible retinal/choroidal lesions, but can also occur in areas without any funduscopical sign of chorioretinal involvement.

Furthermore, choriocapillaris flow voids on OCT-A can also occur in other uveitis entities, which have been described for different pathologies and may serve as markers of disease activity or complications [129–131]. As OCT-A has a minimum blood flow velocity threshold for detection of perfusion, no detected signal on OCT-A needs to be primarily defined as a subthreshold signal. Hence, it does not allow for a differentiation of very slow perfusion, which is not picked up by OCT-A, from no perfusion.

Vasculitis/Capillary Leakage

Retinal vasculitis can be an important sign of activity in various posterior uveitis entities including Behçet's disease, sarcoidosis, tuberculosis, and birdshot retinochoroidopathy. Presence and severity of retinal vasculitis can be assessed clinically by funduscopic examination as well as by color fundus photography (Fig. 4, perivascular sheathing, hemorrhage, vascular occlusions, and cotton-wool spots) and fluorescein angiography (leakage and vascular staining, preferable for assessment of inflammatory activity) [9, 88, 89, 102, 109, 132–135] Vasculitis can be stratified into arterial (arteriolitis) and venous (phlebitis) involvement, and capillary leak-

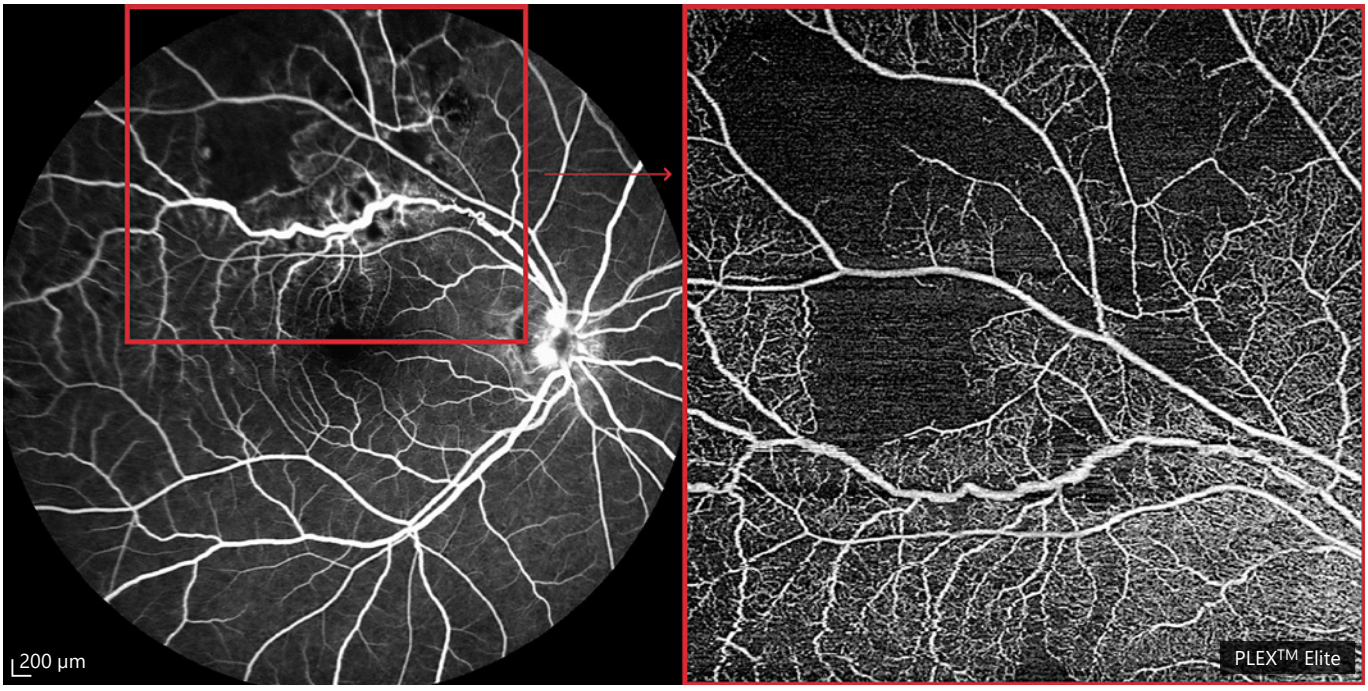

Fig. 5. Assessment of retinal capillary dropout on fluorescein (left; late phase; Spectralis HRA; Heidelberg Engineering) and optical coherence tomography angiography in a case of idiopathic occlusive retinal vasculitis (right; PLEX Elite 9000; Zeiss Meditec).

age can be present diffusely, peripherally, focally, or in certain "patterns" such as the wreath-like hyperfluorescence in MEWDS [101, 103, 108, 118, 136–138]. Vasculitis can also be present in the choroidal stroma, for example, in Vogt-Koyanagi-Harada disease or in sarcoidosis, where leakage can be assessed by indocyanine green angiography [114, 115]. Certain characteristic angiographic findings may be indicative of specific uveitis entities, such as pinpoint leakage on fluorescein and indocyanine green angiography in Vogt-Koyanagi-Harada disease.

Retinal Nonperfusion

Retinal capillary dropout, for example, as a result from occlusive vasculitis, can be examined and quantified on fluorescein angiography and OCT-A (Fig. 5). Automated quantification of retinal nonperfusion on OCT-A is well established [129, 139]. While capillary dropout as a vasculitis sequel is usually a measure of irreversible disease damage, capillary dropout on OCT-A needs to be interpreted with caution. Again, the potential confounding due to subthreshold perfusion needs to be kept in mind when interpreting OCT-A imaging (see above). In addition, retinal atrophy can occur as a common consequence of retinal capillary dropout. While retinal capillary dropout is a common sequel of retinal vasculitis, it can also occur in cases without obvious presence of retinal vasculitis, for example, in intermediate uveitis [38, 129, 140]. In addition, quantification of the microcirculation in the peripapillary area by OCT-A may be a useful indicator for capillary insufficiency and impairment of ocular blood flow as a long-term complication from inflammation [141].

Optic Disc Edema and Inflammation

Optic disc edema is a sign of disease activity and can be assessed and quantified by clinical examination [9], though much more reliably and objectively on fluorescein angiography (as a "hot disc") and OCT [43, 87, 117]. Optic disc hyperfluorescence on indocyanine green angiography is thought to represent an additional measure of disease activity in severe cases [87].

Retinal/Choroidal Neovascularization

Inflammatory retinal/optic disc/choroidal neovascularizations can be complications of various posterior uveitis/panuveitis entities including sarcoidosis, Behçet's disease, punctate inner choroidopathy, multifocal choroiditis, serpiginous choroiditis, and tuberculosis-associated choroiditis and could hence serve as endpoints for disease progression/complication [142–145]. Although the secondary neovascularizations can be detected by fluorescein or OCT angiography, fluorescein angiography remains the reference standard for determining neovascular activity [142, 146–150]. Discrimination of neovascular activity and inflammation from a retinal lesion can be challenging, and OCT and OCT-A can aid differentiation [144, 151, 152]. Moreover, OCT-A can outperform fluorescein angiography in detection of choroidal neovascularizations in certain cases and may offer a valuable instrument for neovascularization follow-up, which could aid monitor treatment [145, 150, 152–155].

Conclusion

To date, numerous different structural outcome measures have been used to assess uveitis inflammatory activity and disease damage, and this considerable heterogeneity in outcomes limits comparability of studies currently available. Stratification for disease *activity* and disease *damage* outcomes is essential, as the former is potentially more relevant for therapeutic management. A new consensus for how disease activity in uveitis should be measured and a consensus on "core outcomes" is warranted. High-priority areas include childhood uveitis and uveitis involving the posterior segment [4, 156–160]. This might not only increase comparability of uveitis trials, but also may facilitate development of guidelines for clinical practice and drug approval and in the end would improve uveitis patient care [4]. In addition, the field would benefit from clear definitions for standardized endpoint assessment, including the unit/scale used for the respective endpoint (e.g., cells/mm^3 for anterior chamber cell quantification) and a clear definition of the anatomic location in which the analysis is performed and of the algorithms used for analyses (as results can vary dependent on the device manufacturer) [16, 161].

Given the enormous amount of available different structural outcome measures employed across different uveitis entities, clear criteria for their evaluation are needed. Important requirements for any endpoint stipulated by regulators and in the available literature are a precise definition, clinical importance, internal consistency in terms of plausibility and validity (is there a true association with visual function and control of disease?), reliability, responsiveness to treatment, and relevance for the respective subtype of uveitis [162–165]. To date, none of the reviewed studies has demonstrated all of this for any of the described outcome measures which highlights that further work is required in this area.

The established endpoints for clinical trials in uveitis are new inflammatory lesions, vitreous haze, anterior chamber cells, and best-corrected visual acuity [165, 166]. However, while visual acuity may be one of the most obvious and natural endpoints for ophthalmic diseases in general, it has been shown to be too insensitive and not relevant for many uveitis cases and is no longer regarded as an appropriate sole primary efficacy endpoint in uveitis [165]. Yet, it is still used by a majority of clinical uveitis trials. All of the clinical ratings lack reproducibility which is problematic for any clinical trial endpoint [18, 156, 157, 167]. This dilemma is reflected in a statement by the European Medicines Agency highlighting the great need for novel endpoints including aspects of structural changes especially in intermediate and posterior uveitis [165].

A general agreement on endpoints is complicated by the extent of possible structural changes on multimodal imaging and the variety of disease-specific findings. Against this background, disease-specific activity scales and endpoints may be appropriate at least in some instances [18]. Endpoints can serve multiple purposes which should be considered when developing or choosing outcome measures including diagnostic, monitoring, and prognostic applications [161].

As highlighted, many of the current shortcomings of outcome measures are determined by the nature of the clinical assessment they are based on. The instrument-based automated methods for endpoint quantification reviewed herein may overcome many of these shortcomings, for example, are better reproducible and also more time and cost efficient compared to manual grading, especially for large studies or datasets [168]. Any development of automated quantification of, for example, intraocular inflammation, would benefit from precise definitions of imaging biomarkers present in uveitis as reviewed here.

In addition to structural outcome measures reviewed herein, functional, patient-reported (e.g., vision-related quality of life), and outcome measures for cost-effectivity analyses are additional important outcome measures also applicable to uveitis trials. In addition, anterior chamber-/vitreous-/serum-based laboratory measures could additionally prove useful as novel outcome measures [169–172]. For example, first studies suggest a possible application of aqueous microRNA analyses in uveitis trials [169, 170]. However, these are still rather experimental and have not been widely implemented in uveitis clinical research.

A commonly used concept is the composite endpoints; however, while composite endpoints can simplify interpretation of clinical trial results, their use remains problematic, as they are often unreasonably combined, inconsistently defined, and inadequately reported [173]. These issues can confound perception of significance of trial results. Therefore, positive composite primary outcomes must be carefully analyzed to determine which components are driving the result [174].

In conclusion, while our review illustrates the multitude of available structural outcome measures, not all might qualify as endpoints for clinical uveitis trials, and thorough testing of applicability is warranted. Although there is a great need for novel, quantifiable structural out-

Table 1. Overview on imaging modalities and their possible use in assessment of uveitis activity and complications

Modality	Assessment of uveitis activity	Assessment of uveitis complications
Optical coherence tomography	**Anterior chamber cells** [14–16] and flare [19, 175], keratic precipitates [35], **vitreous haze** [47–49], **hyperreflective preretinal/ vitreous deposits** [40, 43], **intra- and subretinal fluid** [4, 57, 59, 62–79, 82, 83, 88, 89, 176], **structure of retinal/choroidal lesions** [40, 43, 90–92] [43, 117], **choroidal thickness and reflectivity** [40, 43, 117, 119, 121–127], **optic disc edema** [43, 117]	**Epiretinal membrane** [54], **presence of retinal/ choroidal lesions** [40, 43, 90], cataract [177, 178]
Laser flare-cell photometry	**Anterior chamber cells** [14–16] and **flare** [14, 15, 19, 21, 117, 179–185]	
Corneal endothelial specular microscopy		**Endothelial cell loss** [15, 39, 186–188]
In vivo confocal microscopy	**Keratic precipitates** [15, 23–34, 118, 120]	
Slit-lamp photography	**Keratic precipitates**, endothelial dust, anterior chamber cells and flare, **hypopyon, iris nodules**, **conjunctival injection** [15, 24, 189–192]	**Corneal opacifications, synechiae, iris atrophy, heterochromia, iris depigmentation, cataract** [15, 189–191]
Fluorescein angiography	**Episcleral and scleral perfusion** [15, 36, 37], **macular edema** [85–89, 193, 194], **vasculitis/leakage of retinal vessels** [89, 101–103, 108, 109, 118, 132–138], **optic disc edema** [87]	**Retinal and choriocapillary nonperfusion** [87], **retinal/choroidal neovascularization** [142, 145–150, 152–155]
Indocyanine green angiography	Episcleral and scleral perfusion [37], **presence of choroidal granulomas** [114, 115], **choriocapillary nonperfusion** [87], leakage of choroidal vessels [114, 115], optic disc hyperfluorescence [87]	**Choriocapillary nonperfusion** [87], leakage of choroidal vessels [114, 115], optic disc hyperfluorescence [87]
Optical coherence tomography angiography	**Iris vessel dilation** [38], **choroidal flow voids due to choroidal granulomas** [43, 116–118], **choriocapillary nonperfusion** [38, 40, 128–131]	**Retinal and choriocapillary nonperfusion** [38, 129, 140, 141], **retinal and choroidal neovascularizations** [38, 144, 145, 148–155]
Color fundus photography	**Vitreous haze** [50], **appearance of retinal/choroidal lesions** [9, 135, 192, 195]	**Epiretinal membrane** [54], **presence and size of retinal/choroidal lesions** [9, 135, 192, 195]
Near-infrared reflectance		**Retinal/choroidal lesions** [90, 93]
Ultrasound biomicroscopy	Vitreous opacities [52]	Vitreoretinal adhesions [52], iris-ciliary body dialysis, uveal effusion syndrome, and inflammatory ciliary body detachment [15, 196], ciliary body edema [15, 197, 198]
Fundus autofluorescence	**Appearance of retinal lesions** [95–100, 117]	**Presence and size of retinal lesions** [95–100, 117]

Structural endpoints requiring further evidence are shown in nonbold font. Spectroscopic OCT [17], ocular flare analysis meter [19, 199], double-pass technique [19, 20, 200], vitreous fluorophotometry [51], multicolor imaging [53], and adaptive optics imaging [109–113] are additional imaging modalities requiring more evidence.

come measures, a consensus on endpoint definition, standardization, and "core outcomes" is required first. Available endpoints reviewed herein and their corresponding modalities are summarized in Table 1, and endpoints requiring further evidence are indicated. Out of all modalities used for assessment of the reviewed structural outcome measures, OCT, color fundus photography, fluorescein/indocyanine green angiography, and fundus autofluorescence may represent "core modalities" for reliable and objective quantification of uveitis outcome measures, based on their practical availability and the evidence provided so far.

Conflict of Interest Statement

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Author Contributions

M.W.M.W., R.P.F., U.P., C.H., and A.K.D. conceptualized the project. M.W.M.W. and R.P.F. did the literature review and drafted the first version of the manuscript. All authors critically reviewed the manuscript, gave final approval, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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