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Objective Quantification of Anterior Chamber Inflammation

Measuring Cells and Flare by Anterior Segment Optical Coherence Tomography

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Purpose: To assess the ability of swept-source (SS) optical coherence tomography (OCT) of the anterior segment (AS) to measure anterior chamber (AC) inflammation (both flare and cells) objectively. To compare OCT-derived inflammatory indices with standard techniques.

Design: Prospective evaluation of a diagnostic test.

Participants: Patients diagnosed with anterior uveitis (active or inactive) and controls.

Methods: Participants underwent an AC inflammation evaluation including: clinical cell and flare grading and laser flare photometry (LFP). Uveitis patients were divided into active or inactive uveitis status according to clinical grading. Anterior segment SS-OCT scans were obtained for each participant. Tomographic images were analyzed to count the AC cells, and to calculate to absolute measurements of aqueous signal intensity. The absolute values were compared with the signal measured by the scan outside the eye, generating an optical density ratio (aqueous-to-air relative intensity [ARI] index). Correlations between OCT-derived AC inflammatory indexes and LFP, clinical grading, participant category (active or inactive uveitis, control), age, gender, and central corneal thickness (CCT) were assessed.

Main Outcome Measures: Correlation between OCT-derived AC inflammatory indexes (ARI index and AC cells on OCT) and standard clinical techniques (LFP, clinical cell grading).

Results: Two hundred thirty-seven eyes (70 active uveitis, 97 inactive uveitis, and 70 controls) were included. Anterior chamber cells count on OCT did not differ between inactive uveitis and controls, but was significantly higher in active uveitis compared to the other categories (both $P < 0.0001$). All groups had different LFP (all $P < 0.0001$). Active uveitis had significantly higher ARI index compared with inactive uveitis and controls (both $P < 0.0001$). Interobserver agreement (intraclass correlation coefficient) for ARI index was 0.78. The ARI index correlated positively with age ($P = 0.043$) and negatively with CCT ($P = 0.006$). The ARI index correlated with LFP in the active uveitis group ($P < 0.0001$), but not in the others. Anterior chamber cells on OCT increased among all cell clinical grades ($P < 0.0001$). The ARI index increased among all flare clinical grades ($P < 0.005$).

Conclusions: Anterior segment SS-OCT could be used for a comprehensive assessment of AC inflammation, providing objective measurements of inflammatory cells and aqueous flare. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

The detection of inflammation within the eye, its severity, and its course over time critically influence clinical management decisions in patients with uveitis.[1] For this reason, objective quantification of intraocular inflammation has been a goal of uveitis research for many years. Despite this, the only available objective system (the Kowa laser flare cell meter; Kowa FM700, Kowa Company, Ltd., Nagoya, Aichi, Japan) is not used widely, and intraocular inflammation currently is evaluated using semiquantitative subjective grading systems that have been developed for grading cells and flare in the anterior chamber (AC) and vitreous haze in the posterior segment.[2–7] Unfortunately, interobserver agreement in grading intraocular inflammation remains low, even using standardized parameters, with the aqueous flare quantification being the less reproducible measurement.[8]

Given the importance of reproducible measurement, especially in clinical trials, a number of approaches have been proposed to overcome the limitations of subjective grading. A grading scale based on standardized fundus photographs has been developed for vitreous haze evaluation and is now used widely in clinical trials.[9,10] Furthermore, spectral-domain optical coherence tomography (OCT)

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has been proposed recently as a useful technique for grading vitreous haze.[11] Different authors have suggested that anterior segment (AS) OCT may be useful to visualize and count inflammatory cells in the AC.[12,13] Objective measurement of aqueous flare is possible using the laser flare photometer (LFP), which provides reproducible and accurate measurements of the AC flare and cells and currently is the benchmark technique.[14–17] Its cost and the lack of consensus regarding its clinical usefulness has greatly limited its use.[18]

Optical coherence tomography is widely available and can provide reliable measurements of both vitreous haze[11] and AC cells.[12,13] If OCT could assess AC flare objectively as well, the result would be a single instrument that objectively grades each of the commonly used parameters for assessing intraocular inflammation. The aim of this study was to assess whether swept-source (SS) OCT of the AS can measure AC flare and cells objectively.

Methods

Population

Consecutive patients with uveitis, referred to the Immunology Eye Unit, Arcispedale S.M. Nuova IRCCS, Reggio Emilia, Italy, between December 2015 and February 2016 were enrolled in the study. Eyes of healthy volunteers were recruited during the same period as control participants. Patients with uveitis were included if they met the following criteria: diagnosis of anterior uveitis, ability to understand, and willingness to sign the informed consent forms. Inclusion criteria for healthy volunteers were no history of uveitis, no past ocular or systemic disease that alters blood–ocular barriers, ability to understand, and willingness to sign the informed consent forms. Eyes with corneal changes that prevented high-quality AC OCT image collection also were excluded. The study was conducted in agreement with the tenets of the Declaration of Helsinki and was approved by the institutional review board or ethics committee. Informed consent was obtained from all participants at enrollment.

Clinical Examination

All participants underwent a complete ocular examination including: best-corrected visual acuity (BCVA), intraocular pressure measurement, and slit-lamp biomicroscopy of the AS and posterior segment. Anterior chamber cells and flare were graded clinically using the Standardization of Uveitis Nomenclature (SUN) classification.[1] Clinical data collected included age, gender, uveitis cause, onset, duration, and clinical course. Aqueous flare was measured with LFP (Kowa FM700; Japan). For each eye, the mean value of 7 consecutive measurements was used. Eyes affected by uveitis were divided into 2 groups based on clinical evaluation: inactive uveitis when both AC cells and flare clinically were graded 0, and active uveitis with any other grading score.

Swept-Source Optical Coherence Tomography of the Anterior Segment Image Acquisition

High-resolution SS OCT scans of the AS were obtained from each included eye using a Casia SS-1000 OCT device (Tomey Corporation, Nagoya, Japan). Images were centered at the corneal apex and collected using a scanning protocol of 2 high-resolution cross-scans, each 6 mm in length and depth with 2048 A/B scans. Patients were asked to fixate on an internal target and to keep the eye open for the duration of the scan. In case of frequent blinking, the eyelids were kept open manually without compressing the bulb.

Image Analysis

Vertical scans obtained from each eye were processed using the instrument's in-built software (Tomey Link Exam Viewer version 7F.2) for grading cells and flare. The theoretical axial and lateral resolution of the Casia SS-1000 OCT are 10 and 30 μm, respectively. Previous studies have identified white blood cells reliably as hyperreflective distinct dots within the AC on AS OCT scans.[12] The same definition was used in our study, and cells were counted manually by a trained operator (A.I.), masked to the patient's diagnosis (Fig 1).

Anterior chamber flare was graded indirectly using an analysis of the aqueous brightness intensity (Fig 2). A 200×200-pixels area of the AC, just beneath the corneal apex, was selected on the scan, and its mean brightness value was calculated using an embedded software tool. A similar reading was obtained from a smaller area (100×100 pixels) located in the top right zone of the scan outside the eye (air) and was used as a reference to standardize the brightness parameter. Intensity values for the aqueous and air spaces then were expressed as a ratio (aqueous-to-air relative intensity [ARI] index) and then multiplied by 100 for statistical convenience. The brightness measurements used to calculate the ARI index were performed twice by 2 independent operators (A.I. and E.G.) to assess interobserver repeatability. Corneal thickness was calculated automatically using an embedded software tool in the event that corneal thickness was a confounder altering the ARI index.

Statistical Analysis

Results were analyzed using SPSS software version 23 (IBM Statistics; IBM Corp., Armonk, NY) and the R statistical package version 3.3.1 (R Project; The R Foundation for Statistical Computing http://www.R-project.org). Normality distribution of continuous variables was tested using the Shapiro–Wilk test. For nonnormally distributed parameters, median values and interquartile ranges were used for descriptive analysis, and nonparametric tests were applied for inferential analysis. Differences in BCVA, LFP, number of AC cells on OCT, and ARI index between groups were tested using the Kruskal–Wallis test and the Man–Whitney *U* test with Bonferroni correction for multiple comparisons. In the active uveitis group, the differences in AC cells on OCT, LFP, and ARI index among different grading scores were assessed by Kruskal–Wallis test. The Spearman correlation coefficient was used to test the correlation between ARI index and the other variables. In the active uveitis group, a multivariate regression analysis was performed to determine the predictors of ARI index, after correcting for the nonnormal distribution of ARI index values. Interobserver agreement for the calculation of the ARI index was tested by intraclass correlation coefficient. All tests were 2 sided with a significant value of 0.05.

Results

A total of 237 eyes from 122 participants were included in the study, 167 eyes with uveitis and 70 healthy control eyes. Ninety-seven eyes had inactive uveitis and 70 eyes had active uveitis. Detailed values for age, gender, BCVA, LFP, ARI index,