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Optical Coherence Tomography Evaluation in the Multicenter Uveitis Steroid Treatment (MUST) Trial

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Abstract

Purpose—To describe the evaluation of optical coherence tomography (OCT) scans in the Muliticenter Uveitis Steroid Treatment (MUST) trial and report baseline OCT features of enrolled participants.

Methods—Time domain OCTs acquired by certified photographers using a standardized scan protocol were evaluated at a Reading Center. Accuracy of retinal thickness data was confirmed with quality evaluation and caliper measurement of centerpoint thickness (CPT) was performed when unreliable. Morphological evaluation included cysts, subretinal fluid,epiretinal membranes (ERMs),and vitreomacular traction.

Results—Of the 453 OCTs evaluated, automated retinal thickness was accurate in 69.5% of scans, caliper measurement was performed in 26%,and 4% were ungradable. Intraclass correlation was 0.98 for reproducibility of caliper measurement. Macular edema (centerpoint thickness ≥ 240um) was present in 36%. Cysts were present in 36.6% of scans and ERMs in 27.8%, predominantly central. Intergrader agreement ranged from 78 − 82% for morphological features.

Conclusion—Retinal thickness data can be retrieved in a majority of OCT scans in clinical trial submissions for uveitis studies. Small cysts and ERMs involving the center are common in intermediate and posterior/panuveitis requiring systemic corticosteroid therapy.

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Introduction

Optical coherence tomography (OCT) provides cross-sectional images of the retina with differential reflectivity characterizing the retinal layers and various morphological features. OCT scans have been widely used to objectively assess retinal thickening in clinical trials in various diseases.[1-4] Macular edema traditionally has been assessed using stereoscopic color photographs with graders assessing the percentage of elevation within the subfields of the ETDRS grid. [5] OCT scans have changed macular edema assessment options by providing an objective measure of the retinal thickening using a similar grid with subfields.[6] In addition,OCT allows identification of intraretinal fluid in the form of cysts and subretinal fluid. The cross-sectional imaging also is advantageous for assessment of vitreoretinal interface abnormalities. Retinal distortion due to epiretinal membrane (ERM),and adherence of the posterior vitreous surface can be well characterized. [7]

The Multicenter Uveitis Steroid Treatment (MUST) Trial is an ongoing study to compare standardized systemic therapy versus fluocinolone acetonide implant therapy for the treatment of active or recently active (within 60 days) cases of non-infectious intermediate uveitis, posterior uveitis or panuveitis.[8] One of the goals of the study is to evaluate the incidence and outcomes of major ocular complications of uveitis. In the MUST Trial, imaging modalities including color photographs, fluorescein angiography, lens photographs and time-domain OCTs are used in a standardized fashion to assess the ocular complications. Here,we report the reproducibility of the evaluation method and baseline OCT features in the MUST Trial.

Methods

Imaging protocol

OCT images are obtained using the Stratus OCT-3 (Carl Zeiss Meditec, Dublin, California). All OCT operators and OCT machines are certified by the University of Wisconsin Reading Center. OCT scans are acquired using the fast macular scan protocol (128 A scans/B scans; 6.0 mm line length; 6 radial scans) and processed through the ‘retinal map (single eye)’ and ‘retinal thickness (single eye)’ analysis programs in the Stratus software (Carl Zeiss Meditec, Dublin, California). Additional high resolution scans are captured using the cross hair scan protocol (512 A scans/B scan) and processed to generate a vertical and horizontal B scan using the ‘align process’ algorithm in the Stratus software. The operators performed a preliminary quality check on the OCT scans before submitting to the Reading Center. Due to the lack of commercially available standalone review software at the time of this study, paper prints of the fast macular retinal map thickness report—the six retinal thickness reports showing the six radial B scans and two align process reports with the vertical and horizontal cross hair B scans—were submitted to the Reading Center. To ensure consistent, standardized data capture throughout the life of the study, the study leadership decided not to shift to digital or to spectral domain OCT evaluation during the course of the study. Subject identifiers other than a study number were removed from all images in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Grading methodology

At the Reading Center, OCT evaluation is performed by trained and certified non-physician ocular disease evaluators (graders). All OCT scans are evaluated independently with no reference to any other visit or the results of any other imaging modality from the same visit. Each OCT scan is evaluated by a single evaluator. The evaluation procedures consisted of 3 parts; the check-in process, quality scoring and morphological assessment. The check-in process consists of a careful verification that the images had been taken in accordance with

the scan protocol and that all required paper prints had been submitted. If verification indicates a problem, queries are sent to the clinical sites either for a repeat scan or a repeat submission, if possible.

Quality scoring of the OCT scan involves a detailed assessment of the map report and the B scans for evidence of image artifacts that could affect the retinal thickness data.[9] B scans are reviewed to look for artifacts that could affect central subfield thickness; e.g.,errors in the segmentation algorithm (boundary line errors) and inaccurate centering of the macula within the B scan (decentration). A score of Good, Fair, Borderline or Ungradable is given based on this assessment. A score of Good indicates that no artifacts are present and all the automatically generated retinal thickness data can be used. In order for an OCT scan to be considered of Good quality,the additional features required are: signal strength of 5 or greater and a standard deviation of less than 10% for the center point thickness. Fair indicates that one or more of the non-central subfields contains inaccurate data. In these cases, the central subfield thickness and centerpoint thickness are utilized and the unreliable non central subfields are discarded. Borderline indicates that the central subfield and automated centerpoint thickness are unreliable and a manual measurement for the centerpoint is required (Figure 1). Ungradable score is given when the central subfield and automated centerpoint are unreliable and a manual measurement of centerpoint thickness cannot be performed. The reason for the borderline or ungradable quality, such as poor signal strength or presence of a confounding abnormality, is noted. Manual measurement of centerpoint thickness is performed on the paper prints of the retinal thickness reports using a handheld digital caliper (Product 9900; Precision Graphic Instruments Inc, Spokane, Washington) after computing a scale factor. [9]

Morphological assessment includes assessment of presence and lateral extent of cysts, and subretinal fluid. Cysts are defined as rounded, non-reflective or minimally reflective spaces withinin the intraretinal layers and include the following features: at least 2mm in size on the B scan, rounded in shape,well defined walls with at least 75% of the wall discernable, with reflectivity comparable to the vitreous. Subretinal fluid is a well defined, non –reflective,bell shaped space between the posterior boundary of the neurosensory retina and the RPE. Lateral extent is categorized into involvement of central 1mm (central subfield) alone, involvement of central 2 mm or extension of cysts beyond central 2mm. In addition, the axial diameter of the cyst at the centerpoint is categorized as small (≤ 200 μ),medium(201 – 400μ) or large (> 400μ). The height of subretinal fluid at the centerpoint is measured with calipers similar to centerpoint thickness. The type of vitreoretinal interface abnormality is identified; epiretinal membrane (ERM) with and without vitreomacular traction and macular hole. If present,their location within and outside the central subfield is categorized.

Intergrader agreement is assessed on a quarterly basis to ensure good quality control. Approximately 5% of images are randomly selected and re-graded every quarter by all four graders participating in the MUST Trial. Intergrader agreement is assessed as the percentage of agreement using kappa statistics for categorical variables and intraclass correlation coefficients for continuous variables.

Results

Of the 479 baseline eyes,OCT images were not available for 26(5.4%) eyes. OCT scanning was not performed in eyes with poor dilation secondary to synechiae, dense cataracts or vitreous opacities. Of the 453 OCT images, 315 (69%) were of good or fair quality (see Table 1). Caliper measurement of centerpoint could be performed in 119 (26%). Boundary line errors and decentration were the primary contributors to automated centerpoint thickness errors. Although this study of severe uveitis cases included many patients with

media opacities, which interfered with photographic grading more frequently,[8] center point thickness data were measureable in all but 19 (4%) of the 453 scans performed. Poor signal strength was the most common cause for ungradable quality. Confounding abnormalities such as macular hole (2 eyes) and vitreomacular traction (2 eyes) were the reason for missing data in 4 scans.

The mean centerpoint thickness was 268 (SD 185) um with 36 % of eyes qualifying for the definition of macular edema (centerpoint thickness ≥ 240 um). [8]

Morphological features are tabulated in Table 2. Cystoid spaces were present in 166 (37%), absent in 264 (58%), and ungradable in 23 (5%). Almost 86% of cysts involved the central subfield and most eyes had small cysts (<200 microns in diameter). Subretinal fluid was seen in <1% of scans. ERMs were seen in 126 (28%) of eyes, mostly involving the central subfield.

Regrades were performed on 78 baseline OCT scans. Intergrader agreement for the categories of quality and morphological evaluation was substantial (Table3). Agreement on quality score was 88% (k =0.78). Of the 78 images, 16 required caliper measurement. The intraclass correlation between the original grade and the regrade for caliper measured centerpoint thickness was 0.98.

Discussion

Central retinal thickness is an important endpoint for various clinical trials with macular edema, and is an important parameter in the clinical management of macular edema. Image artifacts affecting automated retinal thickness measurements are not disease-specific, but the frequency of the artifacts varies with the disease.[10,1112] In a large series of 3,794 OCTs with diverse retinal pathology, automated central retinal thickness was erroneous in 16% of scans in diabetic retinopathy,24% in vein occlusion and 55% in wet macular degeneration. [10] Evaluation for structural changes showed that 10% of scans could not be interpreted in eyes with uveitis. [13] Detailed evaluation of OCT quality has not been reported previously for eyes with uveitis, which is known to potentially result in macular edema, ERM and tractional changes,[14] and a propensity towards media opacity. OCT Evaluation in the MUST Trial using a standardized protocol with evaluation at a central Reading Center showed that automated retinal thickness measurements were inaccurate in more than 30% of scans, demonstrating that simple use of the automated measurements is not adequate for research or clinical practice. However, manual measurement of thickness in cases with decentration or boundary line errors resulted in measurable thickness in nearly all cases, despite a high prevalence of cataract and vitreous haze in this uveitic population. [8] Our estimate that approximately 5% of eyes could not be scanned and 96% of eyes can be graded is useful in calculating the expected sample size when OCT-measured central retinal thickness data will serve as a key endpoint in clinical studies.[15]

Understanding the extent and pattern of artifacts observed in the setting of uveitis also is important to improve future iterations of the OCT software. In the time-domain OCT dataset from the MUST Trial, artifacts affecting the central retinal thickness measurement algorithm were more frequent than in diabetic macular edema and retinal vein occlusions.[10] Boundary line errors accounted for almost 50% of scans with inaccurate automated central subfield thickness. Errors in inner boundary lines might be attributable to the higher frequency of ERMs, retinal traction and poor signal strength resulting from media opacity in severe uveitis cases (Figure 1 top). Errors in the outer boundary lines were due to changes at the level of the retinal pigment epithelium (RPE) such as scars, hard exudates, and fibrosis (Figure 1 bottom). The frequency of decentration also was higher than in clinical trials of

diabetic retinopathy or retinal vein occlusion[10], perhaps because a number of participants had poor visual acuity, non dilating pupils, lens opacities, vitritis, and/or disruption in macular anatomy due to pigment changes, scarring and media opacities, all of which could hinder centration.

The quality scoring system represents the accuracy of the automated central retinal measurements. A B scan with poor quality can still be evaluated for morphological changes. Despite the media problems described above, the number of scans with ungradable morphological data was <5% in the MUST Trial. The mean retinal thickness for the baseline OCT scans in the MUST trial was 268(+/−185)μ for intermediate and posterior/panuveitis cases.[8] 36% of eyes had macular edema at baseline, defined as a center point thickness ≥ 240 um. Characterization of the edema showed predominantly small cysts in the center. This is contrary to the distribution of edema described by Castellano et al for cases of iridocyclitis, where the edema was located predominantly in a ring around the center, perhaps reflecting the different sites of inflammation studied. In contrast to the report of Markomichelakis et al, in which 20% of 84 uveitic eyes with macular edema had subretinal fluid,[14] fewer than 1% of MUST Trial cases had subretinal fluid. The higher frequency of subretinal fluid compared to the MUST trial could be attributed to the more severe baseline macular edema with a mean retinal thickness of 333(+/−171) μ. ERMs were also slightly lower in the MUST dataset (28% vs.40%). A difference in the methodology, specifically inclusion of globally adherent ERMs could attribute to this.[7] The Reading Center methodology defines ERM as a hyper-reflective layer with a bridging effect over the inner retinal layers. This definition potentially excludes globally adherent ERMs if their reflectivity merges with that of the nerve fiber layer. Corrugation of inner retinal layers is also considered insufficient to identify an ERM. These detailed definitions are essential to maintain good intergrader agreement in clinical trials where evaluation is masked to other imaging modalities; i.e. OCTs are graded without information from color photographs. The agreement was substantial (k=0.67) for the presence and location of ERMs in the MUST trial.

Although the MUST trial employed time domain OCT, the data derived from this technology is still useful in the era of spectral domain OCT (SDOCT). Standardized data from such a large number of uveitis cases with a two year follow-up period is not yet available with SDOCTs. Studies have shown a lower frequency of artifacts with SDOCT but the types of artifacts largely remain the same[16, 17]. Thus,our results indicating that macular thickening can be imaged in the large majority of severe uveitis cases suggest that SDOCT is likely to be highly effective in imaging macular thickening in the uveitis setting. The reduced sampling of the macular area with time domain OCT may limit the evaluation of ERMs, requiring input from other imaging modalities to accurately diagnose this condition, whereas the high scan density, three dimensional viewing and higher resolution of SDOCT provide improved ability to visualize vitreoretinal surface abnormalities. [18]

In summary, the time-domain OCT evaluation method used in the MUST trial is reproducible. Quality determination, with manual measurement in cases with boundary line errors or defective centration, is an integral part of OCT evaluation when retinal thickness data are used as clinical trial endpoints. In the majority of cases, retinal thickness data can be accurately obtained, even when a large number of eyes with compromised media and inflammatory macular injury are included. Macular edema in recently active intermediate and posterior/panuveitis most commonly is characterized by small central cystoid spaces.

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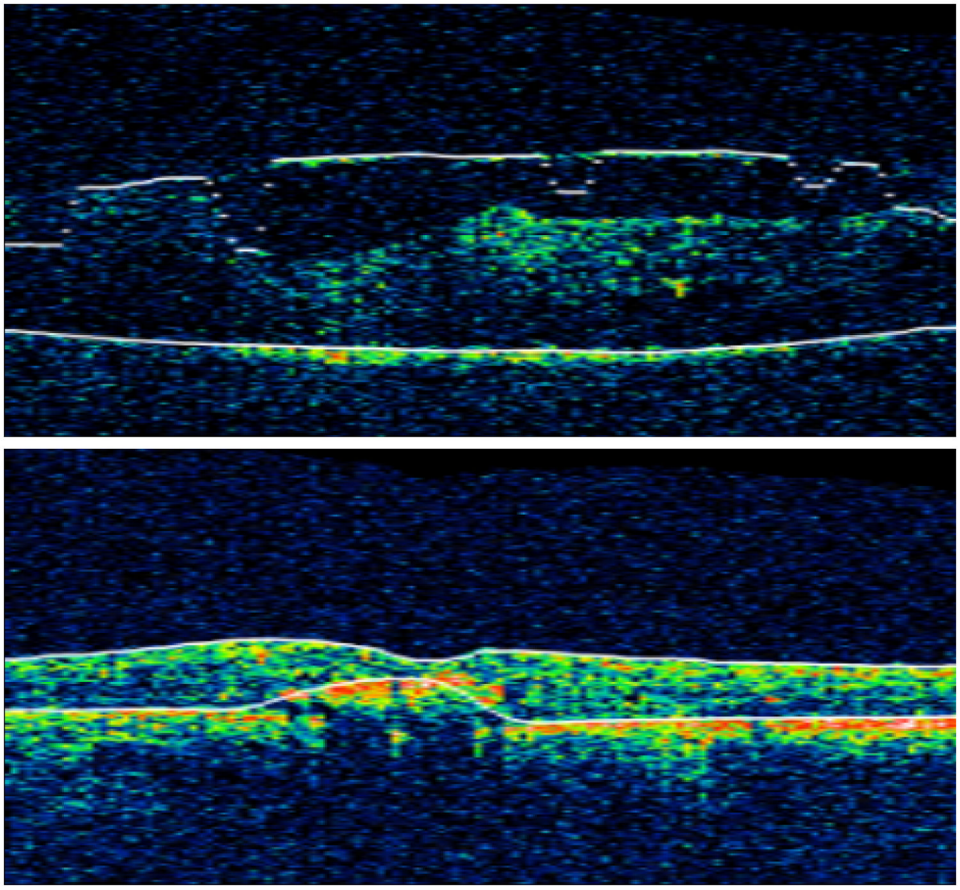

Figure 1.
Inner boundary line errors in an OCT with epi-retinal membranes and poor signal strength (above) and outer boundary line errors in an OCT with intra-retinal hyper-reflectivity (below).

Table 1
Quality evaluation of baseline Optical Coherence Tomography (OCT) scans

Quality score	N=453	%
Good	282	62.2%
Fair	33	7.3%
Borderline	119	26.3%
Decentered alone	23	19.3%
Boundary line error	58	48.7%
Both of the above	15	12.6%
Others	23	19.3%
Ungradable	19	4.2%
Poor signal strength	12	63.2%
Scan protocol issue	3	15.8%
Confounding lesion	4	21.0%

Table 2
Morphological evaluation of baseline OCT images

Morphological characteristics	N=453	%
Cystoid spaces present	166	36.6%
Within central subfield alone	43	25.9%
Within and outside central subfield	100	60.2%
Outside central subfield	23	13.9%
Cyst diameter at centerpoint	108	23.8%
Small ≤200 μ	55	50.9%
Medium 201-400 μ	27	25.0%
Large >400 μ	26	24.1%
Subretinal fluid	4	<1%
Epiretinal membranes	126	27.8%
Involving central subfield	83	65.8%
Vitreo macular traction	3	2.4%

Table 3
Intergrader agreement for OCT evaluation variables (n= 78)

OCT variable	Agreement n (%)	Kappa (95% confidence interval)
Quality Score	69 (88%)	0.78(0.65 –0.91)
Manual measurement of centerpoint	72(92%)	0.83(0.7 – 0.96)
Cystoid spaces	64(82%)	0.66 (0.5 – 0.81)
Epiretinal membrane	61(78%)	0.67 (0.49–0.85)