

RESEARCH PROTOCOL

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Date 10/6/2016

Research Title: Objective, Prospective Measurement of Anterior Chamber Cell Grading Using Anterior Chamber Ocular Coherence Tomography

Short Title: Prospective OCT Measurement of AC Cells

Purpose:

- To determine the feasibility of objective measurement of anterior chamber (AC) cell count utilizing
 - the SPECTRALIS (Heidelberg Engineering, Franklin, MA) spectral domain optical coherence tomography (OCT) system
 - the iSCAN (Optovue, Fremont, CA) spectral domain OCT system
- To develop algorithms that automatically differentiate between cells and “noise” in the anterior chamber OCT (AC-OCT) images and objectively measure the cell density
- To correlate the objective AC cell density measurement and the subjective clinical AC cell grading
- To compare the objective AC cell density measurement with subject treatment outcomes

Introduction:

Treatment decisions for patients with uveitis are currently formulated largely on subjective clinical exam data with high interobserver variation.¹ The most used and most accurate of these subjective clinical data is anterior chamber (AC) cell grade, a measure of intraocular inflammation.¹ AC cell grade is measured by experienced clinicians who manually count the number of leukocytes in a 1mm by 1mm beam of light in the AC visible through a slit lamp stereoscope. The result is a “grade” for AC cells on a nonlinear, ordinal scale as follows: grade 0 is <1 cell, grade 0.5+ is 1-5 cells, grade 1+ is 6-15 cells, grade 2+ is 16-25 cells, grade 3+ is 26-50 cells, and grade 4+ is >50 cells.² The wide range of cells included in the higher grades means that a large change in anterior chamber inflammation might go unnoticed. For example, a patient with 28 cells at their last visit (grade 3+) but 48 cells at their current visit (still grade 3+) would have their 71% increase in intraocular inflammation go unnoticed, as they are still grade 3+. This has concerning implications for both the treatment of patients with intraocular inflammation and the evaluation of interventions that target intraocular inflammation (such as pharmaceuticals).

People with uveitis and people who recently underwent cataract extraction surgery often have intraocular inflammation on clinical exam. Those with uveitis are generally given anti-inflammatory medication to resolve their inflammation. Inflammation after cataract extraction surgery is generally self-resolving.

Optical Coherence Tomography (OCT) uses infrared light with a central wavelength of 840 - 870 nm from a superluminescent diode to scan ocular structures and produce cross sectional and three dimensional images.^{3,4} It is considered a Class 1 laser product that, “does not pose any safety hazard whatsoever.”^{3,5}

RUTGERS APPROVED
THE STATE UNIVERSITY
OF NEW JERSEY

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OCT machines are used widely in ophthalmology clinics to image the retina and objectively measure glaucoma progression. It can also be used to image the anterior chamber.

A few studies have evaluated the feasibility of imaging the AC to objectively measure intraocular inflammation using optical coherence tomography (OCT). Many of these have used older, time domain OCT (TD-OCT) devices, with resolutions larger than most leukocytes.⁶⁻⁸ One has used newer, spectral domain OCT (SD-OCT) technology with promising results.⁹ No study that we are aware of, however, has either used the SPECTRALIS or iSCAN SD-OCT systems for these measurements, or correlated these measurements against clinical outcomes. We plan to use the SPECTRALIS and iSCAN SD-OCT systems to image the AC of subjects with intraocular inflammation, automate the objective reading of AC cell count from these images, correlate the objective count with the subjective clinical grade, and observe if the correlation is strong enough to guide treatment decisions.

Hypothesis:

Automated, objective measurement of anterior chamber cell count with the SPECTRALIS (Heidelberg Engineering, Franklin, MA) and iSCAN (Optovue, Fremont, CA) spectral domain optical coherence tomography systems cannot be used to guide the treatment of patients with intraocular inflammation.

Methods:

This is a prospective clinical imaging study. Treatment and follow up of subjects will not be altered through this study. Subjects will be selected from the pool of patients in the Doctors Office Center (DOC) at New Jersey Medical School/University Hospital who attend the Wednesday Uveitis clinic. The clinic is staffed by two staff physicians (David Chu, MD and Ronald Rescigno, MD) and a rotating staff of NJMS ophthalmology residents. Non-patient control subjects may also have an opportunity to participate in this study; this group will include friends and relatives of enrolled subjects and any person who volunteers for the study (such as those who saw the study registered on clinicaltrials.gov). Up to 300 subjects will be enrolled.

Three groups of subjects will be enrolled: one “uveitis imaging” group, one “cataract imaging” group, and one “control” group. The uveitis imaging group will include subjects with uveitis. The cataract imaging group will include subjects who have just undergone cataract extraction surgery within the previous 30 days. The third group will function as a control. Inclusion criteria for both imaging groups will include an age over 18 years old and active anterior chamber inflammation in at least one eye as diagnosed by clinical exam. Inclusion criteria for the uveitis imaging group will also include a diagnosis of uveitis. Inclusion criteria for the cataract imaging group will also include having recently undergone cataract extraction surgery within the previous 30 days. Inclusion criteria for controls will include an age of 18 years old in subjects with and without uveitis who do not have active intraocular inflammation based on clinical exam. Exclusion criteria for all three groups will include corneal opacities in the affected eye that would limit objective measurement by OCT and anyone judged unable to understand or consent to study participation. The two staff physicians will identify eligible subjects for inclusion. Controls will be recruited from the same clinic described above. Controls will include patients who meet the inclusion criteria above, and also non-patient control subjects who meet the inclusion criteria above.

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Prior to the scan, non-patient control subjects will also undergo a brief, non-contact ocular exam by either David Chu, MD or Ronald Rescigno, MD, to ensure that they meet inclusion and do not meet exclusion criteria (e.g. they have no intraocular inflammation and no corneal opacities); this exam will not require any eye drops.

The study will be thoroughly explained to any potential subjects identified by the two staff physicians. Subjects recruited will be patients of the investigators or non-patient control subjects (such as the relatives and friends of those patients who attend the clinic with them). Any potential subject will be asked to participate and will have the study thoroughly explained to them. They will have the opportunity to ask questions and will be given ample time to decide on participation or nonparticipation. They will also have the opportunity to discuss the study and their participation with relatives or friends. They will be notified that their participation is completely optional and that participation or nonparticipation in this study will not alter or affect their relationship with their doctor or any of their healthcare providers. To avoid coercion, the study risks will be carefully explained to subjects and it will be emphasized that participation is completely optional and not required for their medical care or for their relationship with their physician. A subject's participation or nonparticipation in this study will not alter or affect their medical care in any way. Treatment of subject's uveitis will still be based on clinical examination, and not on any information obtained from the OCT imaging. The consent process will be administered by any of the following study staff ("study personnel obtaining consent"): Elliot Crane, study coordinator and NJMS medical student; David Chu, MD and uveitis specialist; and Ronald Rescigno, MD and uveitis specialist.

The study personnel obtaining consent will ensure each subject has verbal fluency of the English language and is well able to understand the study procedures and consent form. People of all economic classes and educational levels will be invited equally to participate in the study. Minority status will also not be a factor in participation. Children, prisoners, and pregnant woman will not be included in this study. Pregnant woman will not be included due to the majority of expected eligible patients being non-pregnant.

The study personnel obtaining consent will assess capacity. Only subjects who have capacity to consent will be allowed to participate. The study personnel obtaining consent will also assess subjects' comprehension of the study. Only subjects who fully comprehend their role in the study will be allowed to participate. Subjects who do not understand their role and the risks and benefits will be ineligible to participate. This includes subjects with significant cognitive impairments and who do not speak English. Subjects with hearing impairments will be allowed to participate as long as they can understand their role in the study and understand explanations from the study personnel obtaining consent. Subject's continued capacity for consent will be monitored by the study personnel who obtain consent. They will be reminded before each image acquisition that they do not have to participate and that they can drop out of the study whenever they want to. The principal investigator may discontinue the study with any subjects who are unfit to participate.

The OCT scan will be taken by either the SPECTRALIS or iSCAN OCT systems, or both. The SPECTRALIS is owned by Rutgers University, and it is stored in a locked room in DOC 6136. The iSCAN is owned by

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Rutgers University, and it is stored in a locked room in DOC 6100A. The image for both OCT systems will be taken by Elliot Crane, the study coordinator and NJMS medical student, who has extensive experience operating various OCT machines and has been trained in operating the SPECTRALIS and iSCAN.

Subjects who meet inclusion criteria, do not meet exclusion criteria, and who agree to participate in the study will be asked to sign a consent form. Non-patient control subjects will then be given a non-contact ophthalmic exam by either David Chu, MD or Ronald Rescigno, MD. All subjects will then be taken to one of two OCT imaging rooms (DOC 6136 or DOC 6100A), where the process of imaging will be explained and carried out. The scan itself will take less than one minute. After consent is obtained, the entire imaging process will take approximately 10-20 minutes. The consent and imaging process will occur at the end of the subject's normal exam visit. The consent, exam, and imaging process for non-patient control subjects will occur at pre-scheduled times arranged individually by the subjects and study staff.

Choice of which OCT system to use (SPECTRALIS or iSCAN) will depend on OCT and subject availability. Subjects will generally be asked to use the SPECTRALIS OCT system. If the SPECTRALIS is being used for clinic patients, subjects will be asked to instead use the iSCAN system. If they have time and agree, some subjects will be asked to use both systems to ensure similar results can be obtained from each system. The system used on a subject's first visit will determine which system they use for their entire enrollment. Subjects will use the same OCT system for the duration of their enrollment in this study.

Each enrolled subject will be scanned a total of between one and eight times over a period of two to eight weeks, depending on the dates of their scheduled follow up visits in clinic. The scans will only occur on their regularly scheduled clinic visits. The first scan will occur on the first visit where they are identified as eligible and they agree to participate. Patients with active intraocular inflammation in the uveitis clinic are generally prescribed anti-inflammatory medications and asked to return within a few days to weeks to evaluate resolution of the inflammation. Patients who recently underwent cataract extraction surgery are also asked to return within a few days to weeks to follow up the surgery. On these follow up visits, the subjects will be reminded that participation is optional and they will be asked to undergo another OCT scan. Subjects who agree will be scanned again on these follow up visits with the same procedure described above. This will allow us to identify both inflammation and resolution of inflammation on the study images and analyze the data as described in the last paragraph of this protocol. Non-patient control subjects will have the option of only undergoing one scan or individually scheduling follow-up visits for repeat scans for up to eight total scans over a period of two to eight weeks. No subject will be scanned more than eight times in total for this study.

The scans performed by the SPECTRALIS and iSCAN OCT machines are non-contact procedures that use safe, infrared light. The subject rests their chin and forehead into plastic rests that are cleaned with alcohol between each use. The SPECTRALIS or iSCAN OCT can then image the subject's eye. The subject's eye will not be touched for this scan or for any part of this study. No eye drops will be used for this study, as none are required for these high quality, non-contact scans.

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All study activities will be performed in the Doctor's Office Center suite 6100. Subject recruitment and the consent process will occur in exam rooms owned by Rutgers University in DOC 6100. Subjects who enroll in the study, as described above, will be brought to either DOC 6136 or DOC 6100A, where the SPECTRALIS OCT or iSCAN OCT, respectively, are stored and where the study scans will be performed; this room and the equipment are owned by Rutgers University. Data storage and analysis will take place on computers and in locked areas of DOC 6100 owned by Rutgers University.

A list of participating subjects with unique identification keys will be kept in the locked room of a secondarily locked research area by the study coordinator.

Data taken from the medical record will include: name, date of birth, medical record number, inflammation status, and ocular history. The name, date of birth, and medical record number will be used to coordinate scans for subject's follow-up visits. The inflammation status and ocular history will be used to make appropriate comparisons for the study.

Scan data will be stored in the SPECTRALIS or iSCAN OCT systems as is standard for clinical practice. Scan data will be taken from the OCT system via encrypted USB drive upon each subject's completion in the study. The data will then be de-identified, labeled with the unique identification key described above, and stored in the locked room of a secondarily locked research area. The key will remain on paper in a locked room in a secondarily locked research area in the DOC. Only the study coordinator and principle investigator will have access to the data.

Subject risks include potential breach of confidentiality of information collected and the loss of 10-20 minutes of time required to complete the OCT scan process. The risk of breach of confidentiality of information is minimal due to the lack of collection of sensitive information and will be further minimized by storing data in locked and password protected files, as described above. Subject benefits include potentially increased understanding of intraocular inflammation and the new management standards that may be applied to their, and others', uveitis treatment in the future.

All subject data obtained will be confidential. Data will only be released in aggregate and no subjects' personal identifiers will be revealed.

De-identified image data from the SPECTRALIS and iSCAN OCT systems will be analyzed two ways. The first analysis methodology will be the manual identification of leukocytes on the OCT image by the staff uveitis specialists. The second analysis methodology will be the automatic identification of leukocytes on the OCT image by computer algorithm. The AC cell count results of the two analysis methodologies will be compared to subject's clinical AC cell grading. Statistical analysis using T-test and other statistical tools will be used to compare the study and the clinical AC cell count methodologies. Study AC cell count results will also be correlated with the actual subject treatment plans and outcomes to test the null hypothesis that the study results would not have been able to correctly guide subject treatment decisions.

References:

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