SECOND UCLA / AMERICAN UVEITIS SOCIETY
INTERNATIONAL WORKSHOP ON

Objective Measures of Intraocular Inflammation for Use in Clinical Trials

AMERICAN UVEITIS SOCIETY

UCLA Stein Eye Institute | DOHENY EYE INSTITUTE

September 27-28, 2024

UCLA Stein Eye Institute
Los Angeles, CA

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AMERICAN UVEITIS SOCIETY | UCLA Stein Eye Institute | DOHENY EYE INSTITUTE

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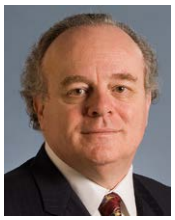

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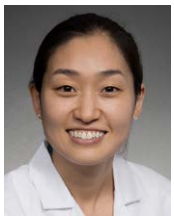

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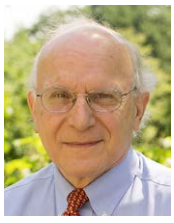

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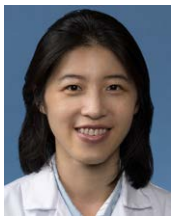
ADDITIONAL UCLA FACULTY



Judy L. Chen, MD
UCLA Stein Eye Institute
Los Angeles, CA

Scott M. Whitcup, MD
UCLA Stein Eye Institute
Irvine, CA

Friday, September 27, 2024

7:00 AM – 5:30 PM
Registration

7:00 AM – 3:00 PM
Exhibits

7:00 – 7:30 AM
Breakfast at UCLA Jules Stein Eye Institute

7:30 – 7:45 AM
Welcome and Introductions
Anne L. Coleman, MD, PhD,
Director of the UCLA Jules Stein Eye Institute
Russell W. Read, MD, representing the
American Uveitis Society

7:45 – 8:00 AM
Introduction: Background, Goals, and Review of Proposed Outcome Measures From Previous Workshops
Gary N. Holland, MD

8:00 – 8:25 AM
Pushing Boundaries through Data Science, Standards, and Collaboration: Perspectives from the National Eye Institute
Keynote Lecture
Michael F. Chiang, MD

8:25 – 8:30 AM
Q&A

8:30 – 8:55 AM
Imaging Ocular Inflammation: Outcomes for Clinical Trials
Guest Speaker
Douglas A. Jabs, MD, MBA

8:55 – 9:00 AM
Q&A

9:00 – 9:20 AM
Challenges in Grading Ocular Inflammation
Guest Speaker
Nisha Acharya, MD, MS

9:20 – 9:25 AM
Q&A

9:25 – 10:30 AM
SCIENTIFIC SESSION 1: ANTERIOR CHAMBER CELLS
Moderators: Cecilia S. Lee, MD, MS &
Ameenat L. Solebo, PhD, FRCOphth

9:25 – 9:35 AM
Development of the Advised Protocol for OCT Study Terminology and Elements Anterior Segment OCT Extension Reporting Guidelines: APOSTEL-AS
Ameenat L. Solebo, PhD, FRCOphth

9:35 – 9:38 AM
Q&A

9:38 – 9:48 AM
Utilizing Vision Transformers in AS-OCT: A Novel Approach for Quantifying Anterior Chamber Inflammation
Carlos H. Cifuentes González, MD

9:48 – 9:51 AM
Q&A

9:51 – 10:01 AM
A Computable Phenotype for HSV Anterior Uveitis: Operationalizing the SUN Classification Criteria
Andrew C. Kim, BS

10:01 – 10:04 AM
Q&A

10:04 – 10:14 AM
Quantification of Anterior Chamber Cells Through an Image Based Grading Scale
Marc D. de Smet, MDCM, PhD

10:14 – 10:17 AM
Q&A

10:17 – 10:27 AM
Aqueous Biomarkers Identify Immunologic Subtypes and Therapeutic Targets in Uveitis
Lynn M. Hassman, MD, PhD

10:27 – 10:30 AM
Q&A

10:30 – 10:45 AM
Break

10:45 – 11:05 AM
The Reasons Why?
Guest Speaker
Wiley A. Chambers, MD

11:05 – 11:10 AM
Q&A

11:10 – 11:49 AM

SCIENTIFIC SESSION 2: ANTERIOR CHAMBER FLARE

Moderators: Judy L. Chen, MD & Annabelle A. Okada, MD, DMSc

11:10 – 11:20 AM

Chronic Anterior Uveitis in Children: Longitudinal Assessment of Cells and Flare
Gary N. Holland, MD

11:20 – 11:23 AM
Q&A

11:23 – 11:33 AM

Reduction of Laser Flare Photometry Values with Initiation of Infliximab Therapy Among Children with Chronic Anterior Uveitis
Judy L. Chen, MD

11:33 – 11:36 AM
Q&A

11:36 – 11:46 AM

A Prospective Longitudinal Assessment of Aqueous Humor Content in Patients with Uveitis Using Laser Flare Photometry
Edmund Tsui, MD, MS

11:46 – 11:49 AM
Q&A

11:49 AM – 1:00 PM
Lunch

1:00 – 1:20 PM
Statistical Considerations for Endpoint Precision
UCLA Speaker
Scott M. Whitcup, MD

1:20 – 1:25 PM
Q&A

1:25 – 1:45 PM
Perspective on Proposed Use of Objective Measures of Inflammation in Clinical Trials
Guest Speaker
Steven Piantadosi, MD, PhD

1:45 – 1:50 PM
Q&A

1:50 – 2:29 PM

SCIENTIFIC SESSION 3: VITREOUS INFLAMMATORY REACTIONS

Moderators: Andrew D. Dick, MBBS, MD & Scott M. Whitcup, MD

1:50 – 2:00 PM

Assessing OCT-derived Vitreous Dot Index (VDI) as a Novel Marker of Vitreous Inflammation in Uveitis
Rupesh Agrawal, MD

2:00 – 2:03 PM
Q&A

2:03 – 2:13 PM

Ultrahigh-Resolution Optical Coherence Tomography for Vitreous Cell Differentiation in Uveitis Assisted by Artificial Intelligence
Eric B. Suhler, MD, MPH

2:13 – 2:16 PM
Q&A

2:16 – 2:26 PM

OCT-Based Evaluation of Vitreous Haze in the First-Line Antimetabolites as Steroid-Sparing Treatment Uveitis Trial
Edmund Tsui, MD, MS

2:26 – 2:29 PM
Q&A

2:29 – 2:31 PM
Industry Presentation
Kowa Company, Ltd.

2:31 – 2:40 PM
Meeting Announcements

2:40 – 3:00 PM
Break and Transfer to Small Group Rooms

3:00 – 5:30 PM
SMALL GROUP SESSIONS

- **Anterior Chamber Cells**
  Co-Chairs: Cecilia S. Lee, MD, MS & Ameenat L. Solebo, PhD, FRCOphth
  Location: A-Level Conference Room Jules Stein Building
- **Anterior Chamber Flare**
  Co-Chairs: Judy L. Chen, MD & Annabelle A. Okada, MD, DMSc
  Location: 3rd Floor Conference Room Doris Stein Building

- **Vitreous Inflammatory Reactions**
  Co-Chairs: Andrew D. Dick, MBBS, MD &
  Scott M. Whitcup, MD
  Reading Room, 1st Floor
  Jules Stein Building
- **Retinal Vasculitis**
  Co-Chairs: Janet L. Davis, MD &
  James T. Rosenbaum, MD
  Location: 3rd Floor Conference Room
  Edie and Lew Wasserman Building
- **Retinal and Choroidal Lesions**
  Co-Chairs: Rupesh Agrawal, MD &
  Sapna S. Gangaputra, MD, MPH
  Location: Seminar Room, 1st Floor
  Jules Stein Building

5:30 – 6:30 PM
Reception in Switzer Plaza, UCLA Center for the Health Sciences

7:00 – 9:00 PM
Dinner at the UCLA Meyer and Renee Luskin Conference Center
(pre-registration required)

Saturday, September 28, 2024

7:00 AM – 4:00 PM
Registration

7:00 AM – 2:30 PM
Exhibits

7:00 – 7:30 AM
Breakfast at UCLA Jules Stein Eye Institute

7:30 – 7:35 AM
Opening Remarks
Gary N. Holland, MD & Russell W. Read, MD, PhD

7:35 – 7:55 AM
FDA Regulation of Ophthalmic Diagnostic Devices
Guest Speaker
Elvin Ng, BS

7:55 – 8:00 AM
Q&A

8:00 – 8:39 AM
SCIENTIFIC SESSION 4: RETINAL VASCULITIS
Moderators: Janet L. Davis, MD &
James T. Rosenbaum, MD

8:00 – 8:10 AM
Pre-retinal Macrophage-Like Cells as Non-Invasive Biomarkers of Inflammation in Children with Uveitis
Parisa Emami, MD, MPH

8:10 – 8:13 AM
Q&A

8:13 – 8:23 AM
Quantitative Analysis of Retinal Microvasculature Using Retinal Vascularity Index in Patients with Uveitis
William Rojas-Carabali, MD

8:23 – 8:26 AM
Q&A

8:26 – 8:36 AM
Validity of Spectral Domain OCT Angiography for Detection of Retinal Vasculitis
Jila Noorikolouri, MD

8:36 – 8:39 AM
Q&A

8:39 – 8:59 AM
Advancing Data Standardization in Eye Health Care and Research
Guest Speaker
Kerry E. Goetz, MS

8:59 – 9:04 AM
Q&A

9:04 – 9:24 AM
Challenges of Defining Endpoints for Immune Driven Responses to Infection
Guest Speaker
Vishali Gupta, MD

9:24 – 9:29 AM
Q&A

9:29 – 10:21 AM
SCIENTIFIC SESSION 5: RETINAL AND CHOROIDAL LESIONS
Moderators: Rupesh Agrawal, MD &
Sapna S. Gangaputra, MD, MPH

9:29 – 9:39 AM
Optical Coherence Tomography-Based Choroidal Vascularity Index: Tracking Uveitis Progression Over Time
Xin Wei, MD

9:39 – 9:42 AM
Q&A

9:42 – 9:52 AM
Assessing and Following Patients with Birdshot Choroidopathy Using a Portable Handheld Electrodiagnostic Testing Device
Alexander Newman, MD, M.MED, B.App. Sci(Optom)

9:52 – 9:55 AM
Q&A

9:55 – 10:05 AM
Objective AI Quantification of Longitudinal GVF Changes Secondary to Autoimmune and Inherited Retinal Diseases
Osama Elaraby, MD

10:05 – 10:08 AM
Q&A

10:08 – 10:18 AM
Characterization of Retinal Microvascular Abnormalities in Birdshot Chorioretinopathy Using Optical Coherence Tomography Angiography
Aman Kumar, MD

10:18 – 10:21 AM
Q&A

10:21 – 10:40 AM
Break and Transfer to Small Group Rooms

10:40 – 11:30 AM
SMALL GROUP WRAP-UP SESSIONS

- **Anterior Chamber Cells**
  Co-Chairs: Cecilia S. Lee, MD, MS & Ameenat L. Solebo, PhD, FRCOphth
  Location: A-Level Conference Room Jules Stein Building
- **Anterior Chamber Flare**
  Co-Chairs: Judy L. Chen, MD & Annabelle A. Okada, MD, DMSc
  Location: 3rd Floor Conference Room Doris Stein Building
- **Vitreous Inflammatory Reactions**
  Co-Chairs: Andrew D. Dick, MBBS, MD & Scott M. Whitcup, MD
  Location: Reading Room, 1st Floor Jules Stein Building
- **Retinal Vasculitis**
  Co-Chairs: Janet L. Davis, MD & James T. Rosenbaum, MD
  Location: 3rd Floor Conference Room Edie and Lew Wasserman Building
- **Retinal and Choroidal Lesions**
  Co-Chairs: Rupesh Agrawal, MD & Sapna S. Gangaputra, MD, MPH
  Location: Seminar Room, 1st Floor Jules Stein Building

11:30 AM – 12:45 PM
Lunch

12:45 – 1:45 PM
SMALL GROUP SUMMARY PRESENTATIONS
Moderator: Cecilia S. Lee, MD, MS
(10 minutes each)

A representative of each Small Group will present the results of the group's proposals for further study or for incorporation of objective measures into clinical trials.

- Anterior Chamber Cells
- Anterior Chamber Flare
- Vitreous Inflammatory Reactions
- Retinal Vasculitis
- Retinal and Choroidal Lesions

1:45 – 2:15 PM
PANEL: DISCUSSION OF SMALL GROUP PROPOSALS AND Q&A
Moderator: Edmund Tsui, MD, MS
Panelists: Small Group Leaders

2:15– 2:30 PM
Break

2:30 – 2:50 PM
The Roadmap for AI Endpoints in Clinical Trials
Guest Speaker
Aaron Y. Lee, MD, MSCI

2:50 – 2:55 PM
Q&A

2:55 – 3:45 PM
PANEL: STANDARDIZATION, VALIDATION, AND IMPLEMENTATION
Moderators: Gary N. Holland, MD & SriniVas R. Sadda, MD
Panelists: Nisha Acharya, MD, MS; Wiley A. Chambers, MD; Kerry E. Goetz, MS; Vishali Gupta, MD; Douglas A. Jabs, MD, MBA; Aaron Y. Lee, MD, MSCI; Elvin Ng, BS; Steven Piantadosi, MD, PhD; Scott M. Whitcup, MD

3:45 – 4:00 PM
CONCLUDING REMARKS
Phoebe Lin, MD, PhD & Edmund Tsui, MD, MS

4:00 PM
Adjourn

Abstract and Summaries

ANTERIOR CHAMBER CELLS

Development of the Advised Protocol for OCT Study Terminology and Elements Anterior Segment OCT Extension Reporting Guidelines: APOSTEL-AS

Ameenat L. Solebo, PhD, FRCOphth. University College London/Great Ormond Street Hospital.
Co-Author(s): APOSTEL-AS Steering group*
Source(s) of Support: NIHR
Relevant Conflicts of Interest: None

Purpose: Anterior segment optical coherence tomography (AS-OCT) will, and should emerge as the standard of care for disease detection and monitoring for children and adults with uveitis. The current absence of guidelines for reporting OCT studies which quantitatively assess the anterior segment is an obstacle to reproducibility and interoperability. In order to provide this guidance, we aim to extend the existing Advised Protocol for OCT Study Terminology and Elements (APOSTEL) guidelines, to enable inclusion of items applicable to AS-OCT.

Methods: The guideline will be developed through a staged consensus process involving literature review and Delphi consensus exercise across an international multi-disciplinary stakeholder committee. A systematic scoping review (eligibility: primary research with generation of quantitative data from in vivo anterior segment OCT imaging) was used to generate candidate items for the guideline extension, develop a consensus nomenclature for the anterior chamber, and form the expert membership base (eye healthcare professionals, patients, methodologists, statisticians, computer scientists, industry representatives, health informaticists, and journal editors) of the Delphi consensus group.

Results: The systematic scoping review identified 4765 articles published from database inception of which 3214 were eligible. Researchers spanned the globe (e.g. 48% USA, 20% UK, Switzerland and India each 5%). Uveitis research constituted 130 papers (4%), of which 53% were published in the last 5 years. Included articles across all clinical disciplines were used to generate seven additional reporting items. Items on study design, acquisition, data selection and analysis protocol, nomenclature and statistic approach have been presented to the wider membership (622 author emails as identified through the review) for consensus, with inclusion threshold set at 80% consensus.

Conclusion: Clinical implementation of AS-OCT in uveitis will depend on the strength of the cumulative evidence base. The currently underway Delphi consensus exercise and future piloting of the APOSTEL-AS checklist should result in a tool which provides timely support for researchers reporting AS-OCT quantitative imaging in uveitis and other fields (cornea, glaucoma, cataract). This will ensure future standardisation, interoperability and reproducibility of reported work and the creation of shared datasets for future research.

Utilizing Vision Transformers in AS-OCT: A Novel Approach for Quantifying Anterior Chamber Inflammation

Carlos H. Cifuentes González, MD.
Tan Tock Seng Hospital.
Co-Author(s): Carlos Cifuentes-González, Joewee Boom, Laura Gutiérrez-Sinisterra, William Rojas-Carabali, Xin Wei, Joewee Boon, Hnin Hnin Oo, Choo Sheriel Shannon, Alejandra de-la-Torre, Rupesh Agrawal
Source(s) of Support: Research was supported by grants awarded by the National Medical Research Council (NMRC), Ministry of Health, Republic of Singapore grant number NRMC/CSAINV22jul-000 and NMRC/CSAINV19nov-0007. The funders had no role in study design, data collection and analysis, publication decisions, or manuscript preparation.
Relevant Conflicts of Interest: None

Purpose: This study evaluated the utility of a novel vision transformer for Anterior Segment Optical Coherence Tomography (AS-OCT) in grading inflammation in uveitis patients.

Methods: Conducted at Tan Tock Seng Hospital, this multicenter cross-sectional study enrolled 180 participants, including uveitis patients and healthy controls. Comprehensive ocular examinations and AS-OCT imaging were performed at baseline, 6 months, and 12 months. Using a new AI segmentation tool, data on Central Corneal Thickness (CCT), Thinnest Corneal Thickness (TCT), Iris Vascular Index (IVI), and Particle analysis (PA) were analyzed with non-parametric Kruskal-Wallis ANOVA due to non-normal distribution.

Results: Female represent the 50%, with an average age of 53.2 (SD14.4) years. Among these patients, 71.7% had uveitis and 28.3% served as controls. Significant differences were observed in CCT, PA and TCT between uveitis patients and controls, with CCT averaging 555 µm in patients versus 529 µm in controls (P=0.003), and IVI was also significantly higher in patients, averaging 45% in those with uveitis versus 30% in controls (P=0.007). Strong correlations between CCT and TCT, and PA with SUN cell grading (P<0.001).

Conclusion: This vision transformer tool significantly quantified inflammation levels, correlating with SUN grading. The precision of AS-OCT measurements provides an objective method that could enhance clinical assessments and treatment strategies for uveitis.

A Computable Phenotype for HSV Anterior Uveitis: Operationalizing the SUN Classification Criteria

Andrew C. Kim, BS. Roski Eye Institute.
Co-Author(s): Brian Toy, MD; Edmund Tsui, MD; Jessica Shantha, MD; Kareem Moussa, MD; Karen Armbrust, MD; William Rojas Carabali, MD; Rupesh Agrawal, MD; Kiana Tavakoli, MD
Source(s) of Support: None
Relevant Conflicts of Interest: None

Purpose: Data models in healthcare have the potential to drastically improve observational research, especially for rare diseases like uveitis. The purpose of this study was to operationalize the Standardization of Uveitis Nomenclature (SUN) classification criteria for herpes simplex virus (HSV) anterior uveitis into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Methods: The SUN classification criteria for HSV anterior uveitis were used to construct a computable phenotype, or cohort definition, using the Observational Health Data Sciences and Informatics (OHDSI) ATLAS tool. Concept sets, or lists of concepts or clinical events, were created to represent each specific component of the SUN classification criteria and combined using logic operators to construct a phenotype for HSV anterior uveitis. This phenotype was applied to multiple databases, specifically Optum's Clinformatics® Extended Data Mart – Date of Death, to identify patients who met the criteria for HSV anterior uveitis. The effectiveness of each component of the SUN criteria in identifying the patient population was assessed, highlighting the most useful elements and noting those needing improvement.

Results: In our review with Optum's Clinformatics, a total of 399,914 patients met the criteria to enter the cohort of HSV anterior uveitis. Of this entry cohort, 10,858 patients remained by meeting all the inclusion and exclusion criteria of the SUN definition, with the most discriminatory inclusion criterion being evidence of herpes simplex infection in the eye. Of this cohort, 55.8% were female and 44.2% were male with about 86.7% of patients over forty years of age. The criterion of evidence of herpes simplex infection in the eye was encapsulated by three concept sets: a. Positive PCR for herpes simplex on aqueous specimen, b. Sectoral iris atrophy in a patient ≤50 years of age, and c. Herpes simplex keratitis. All included individuals in the cohort for Optum's Clinformatics database demonstrated a history of HSV keratitis, while no patients were found to have been included in the cohort because of a positive PCR for HSV or a condition of sectoral iris atrophy.

Conclusion: These findings suggested that an HSV keratitis diagnosis may be the most significant component of the SUN criteria in identifying patients with HSV anterior uveitis in databases similar to Optum's Clinformatics. The absence of certain clinical data points in administrative claims databases, like PCR results and sectoral iris atrophy, highlights areas where data collection and recording practices may need enhancement to fully utilize the SUN criteria in observation research.

Quantification of Anterior Chamber Cells Through an Image Based Grading Scale

Marc D. de Smet, MDCM, PhD. Tarsier.
Co-Author(s): Ron Neumann, Daphne Haim-Langford, Zohar Milman, Michal Kramer
Source(s) of Support: Tarsier Pharma
Relevant Conflicts of Interest: Tarsier MdS C, DHL E, ZM E, MK C (C consultant; E employee)

Purpose: The exact agreement on gradings by uveitis specialists of anterior chamber (AC) cells using the Standardization of Uveitis Nomenclature (SUN) criteria is low, though it is acceptable if tolerance is increased to +/- one grade. It is particularly high with low grades of inflammation (2 or less), where cell counts are still possible in a reasonable time. Pattern recognition through a visual grading scale can help overcome the limitations of the SUN criteria as the observer is asked to recognize cell density rather than cell count for any given grade. The purpose of this study is to demonstrate the use of a set of computer generated images based on the SUN scale for AC cells, and demonstrate its ability to provide better inter-grader consensus rather than simple observation.

Method: A set of images representing different scores of ACr cell grades were created according to the following scale: Grade 0 – zero cells; grade 1 – 1-5 cells; grade 2 – 6-15 cells; grade 3 – 16-30 cells and grade 4 – more than 30 cells. For each grade, 3 different images were created. The Grading Image Scale (GIS) software was implemented using Python. User software interaction was through an intuitive graphical user interface and fluid transition between (1) test phase in which the user is learning the score mechanics, and (2) main scoring phase in which the user grades randomized images representing different ACC grades. Uveitis experts used the software to grade the different images and the consistency between experts was calculated. The consistency threshold was set to > 75%.

Results: Grading results of 11 uveitis experts were analyzed and the scoring of the images were found to be consistent between experts and above the set threshold. The higher consistency was found for the lower ACC grades of 0, 1 and 2 (98%, 93% and 91% respectively) and lower consistency for ACC grades 3 and 4 (77% and 83% respectively).

Conclusions: An image based grading scale provides a better agreement within each grade compared to the current SUN grading system. Its use in clinical studies would likely improve and standardize further the reporting of anterior chamber cells, by a simple extension of existing practice.

Aqueous Biomarkers Identify Immunologic Subtypes and Therapeutic Targets in Uveitis

Lynn M. Hassman, MD, PhD.
University of Colorado.
Co-Author(s): Christian Concepcion and Yu Xia, Yulia Korshunova, Greg Bligard, Michael Paley, Phil Ruzycki, Lynn Hassman
Source(s) of Support: NEI, RPB
Relevant Conflicts of Interest: None

Purpose: Uveitis is a clinically heterogeneous group of ocular inflammatory diseases for which empiric therapy fails many patients. We hypothesized that pathophysiologic mechanisms differ between patients and may drive differential response to therapy.

Methods: We utilized single-cell transcriptional and immune receptor profiling to analyze the immunologic features in ocular fluid biopsies from 23 patients.

Results: The composition of ocular inflammatory cells varied between patients and was associated with clinically defined uveitis subtypes; disease chronicity within a clinical entity; and therapeutic outcomes. Specifically, aqueous infiltrates from patients with HLA-B27 AAU were enriched in myeloid cell types, while those from granulomatous uveitis were enriched in antigen-activated lymphocytes. Evidence for an antigen-driven immune response correlated with disease chronicity in HLA-B27 AAU. The expression of tumor necrosis factor (TNF)-receptor differed between responders and non-responders to TNF-inhibition.

Conclusions: Deep transcriptional profiling of ocular immune cells can identify patient and disease-specific pathophysiologic mechanisms that may drive inflammation and treatment responses in uveitis. These insights provide a mechanistic framework to understand the variable susceptibility to specific therapies in uveitis. paving the way toward precision treatment strategies.

ANTERIOR CHAMBER FLARE

Chronic Anterior Uveitis in Children: Longitudinal Assessment of Cells and Flare

Gary N. Holland, MD. UCLA Stein Eye Institute.
Co-Author(s): Gary N. Holland, Christopher S Denove; Fei Yu. Ocular Inflammatory Disease Center, UCLA Jules Stein Eye Institute and Department of Ophthalmology, David Geffen School of Medicine at UCLA. Los Angeles, CA. 90095-7000. USA
Source(s) of Support: Endowment for Children with Uveitis, UCLA Jules Stein Eye Institute, Los Angeles, California, the Skirball Foundation, New York, New York.
Relevant Conflicts of Interest: None

Purpose: To describe changes in anterior chamber cells and flare during follow-up of children with chronic anterior uveitis (CAU); and to determine whether time-dependent changes predict subsequent adverse events (AE) during follow-up.

Methods: We performed a retrospective review of medical records for 115 children (206 involved eyes) with non-infectious CAU (disease onset at ≤16 years of age) who were first examined by one author (GNH) during the period 1993-2006. We evaluated the following changes as predictors of AE (incident complications, vision loss to ≤20/50): sustained improvement in cells (2 steps, as defined by the SUN Working Group); sustained reduction of cells below a threshold of 1+; 20% reduction in laser flare photometry values; and sustained reduction of flare below 20 photon units (pu)/msec.

Results: Longitudinal data were available for 86 children (159 involved eyes), with a median follow-up of 33.9 months (range 0.4-172.4 months, 2125 patient visits). There was a statistically significant correlation between changes in cells and changes in flare over time, but the relationship was weak (Pearson correlation coefficient=0.30, $p<0.0001$). Maximum flare values during follow-up were statistically associated with incident complications ($p=0.004$), while maximum cell values were not ($p=0.075$). Both reduced flare and sustained flare below threshold were protective against vision loss (HR=0.32 [95%CI=0.10-1.00], $p=0.051$ and HR=0.14 [0.048-0.40], $p=0.0002$, respectively), but we could not confirm a protective effect of these factors against complications. Improvement in cells and cells below threshold were protective against vision loss (HR=undefined, $p=0.020$ and HR=0.14 [0.034-0.60], $p=0.008$, respectively). Protection against complications was associated with cells below threshold (HR=0.42 [0.21-0.85], $p=0.016$), but not with improvement alone (HR=0.57 [0.23-1.42], $p=0.23$).

Conclusion: Cells and flare can vary independently during the course of CAU in children. Findings are consistent with the notion that, while cells

are indicators of change in status, flare is a better measure of long-term risk of AE. Risk factor analysis supports recommendations that intraocular inflammation be suppressed maximally to prevent vision-threatening complications of uveitis in children.

Reduction of Laser Flare Photometry Values with Initiation of Infliximab Therapy Among Children with Chronic Anterior Uveitis

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Source(s) of Support: Endowment for Children with Uveitis, UCLA Stein Eye Institute, Los Angeles, California, the Skirball Foundation, New York, New York.
Relevant Conflicts of Interest: None

Purpose: Infliximab is a well-established treatment for children with juvenile idiopathic arthritis (JIA), many of whom have chronic anterior uveitis (CAU), but published studies to date about its effect on intraocular inflammation in this population have been difficult to interpret and compare because of differential follow-up and non-standardized outcome measures. In studies of CAU in children, specific time-dependent changes in anterior chamber cells and flare have been associated with a reduced risk of disease-related adverse events (AE). In this study, we describe the course of cells and flare in this population during infliximab therapy.

Methods: In this retrospective study, we reviewed the medical records of 23 children (42 affected eyes) with CAU in a tertiary referral practice who were treated with infliximab. The following information was collected for each case: age at onset of uveitis; sex; associated systemic disease, if present (JIA, other); and duration of uveitis before start of infliximab. The following information was collected from each ophthalmic examination: cells (categorized based on SUN criteria); flare (as determined by laser flare photometry); presence of uveitis complications; and complications attributable to drug infusion. Kaplan-Meier analyses were used to determine intervals to outcome measures for control of uveitis and for loss of control, as defined below. Outcomes for cells and for flare were analyzed separately. For cells, control of inflammation was defined as <1+ cells. For flare, control of inflammation was defined as a 20% reduction (for values greater than 20 photon units per millisecond [pu/msec]) or an absolute value <20 pu/msec; these definitions correspond to levels shown to be protective against AE (uveitic complications, vision loss). The eye was the unit of analysis.

Results: Mean age at uveitis diagnosis was 4.48 years (range 1-10 years), and the mean duration of uveitis prior to start of infliximab was 5.43 years (range 0.75 to 23.25 years). The majority of patients were female (73.9%) and had a diagnosis of JIA (56.5%). Median duration of treatment with infliximab during the study period was 4 years. Median time to decrease of cells to <1+ was 1.9 months (95% CI=0.4-2.8 months, range 0.0-10.4 months); median time to decrease of flare to <20 pu/msec was 1.35 months (95% CI=undefined, range 0.0-112.9 months). The median time to loss of control based on cells (≥1+ after initial decrease to less than 1+) was 5.9 months (95% CI=3.8-8.1, incidence 14.8/100 eye-months); median time to loss of control based on flare (≥20 pu/msec) was 14.0 months (95% CI=undefined, incidence 4.2/100 eye-months). Among study eyes, 9 developed cataracts, and 1 developed posterior synechiae during treatment. Infusion related problems developed in 3 children after 4-14 infusions (anaphylactoid reaction, rash, and pruritus).

Conclusion: This study illustrates the potential use of a standardized, time-dependent assessment of drug effect on CAU in children, using objective measures of inflammation and outcomes shown to be related to disease-associated AE. Cells and flare can change independently, but the majority of patients achieved levels of cells, flare, or both within 2 months that are protective against AE. The study also provides objective evidence that infliximab may lose effect over time, but vision-threatening complications remained infrequent during treatment.

A Prospective Longitudinal Assessment of Aqueous Humor Content in Patients with Uveitis Using Laser Flare Photometry

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Source(s) of Support: Kowa Company Ltd.
Relevant Conflicts of Disclosure: Consultant for Kowa Company Ltd.

Purpose: To evaluate the longitudinal utility of laser flare photometry (LFP) in monitoring patients with uveitis and correlate LFP values with the Standardization of Uveitis Nomenclature (SUN) clinical grades of anterior chamber flare as a surrogate for aqueous humor protein content.

Methods: 100 patients with a history of uveitis prospectively underwent measurement with the FM-500 laser flare photometer (Kowa Company Ltd., Tokyo, Japan) over the course of 1 year at their routine follow-ups. The SUN clinical grade of anterior chamber flare and anterior chamber cell were

recorded at each visit. The change in LFP value was measured longitudinally. LFP values were analyzed using a mixed effect linear regression model.

Results: The results of this study will be presented at the Workshop.

Discussion: Laser flare photometry is beneficial in the monitoring and evaluation of anterior chamber flare in patients with uveitis.

VITREOUS INFLAMMATORY REACTIONS

Assessing OCT-derived Vitreous Dot Index (VDI) as a Novel Marker of Vitreous Inflammation in Uveitis

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Relevant Conflicts of Interest: None

Purpose: This study evaluates the Vitreous Dot Index (VDI) by an Optical Coherence Tomography (OCT) as a biomarker for vitreous inflammation.

Methods: We conducted a cross-sectional study involving 61 patients, examining only the diseased eye in pathological groups and the right eye in 17 controls. Patients were categorized into uveitis (n=20), vitreous degeneration (n=15), and others (n=9). Using the Spectralis system, OCT scans captured the vitreous on a 30° x 30° macular region centered on the fovea, with 19 to 31 B-scans per volume. Semi-automated image segmentation software delineated the vitreous-retinal layer boundary, identified as the internal limiting membrane (ILM), which was manually fine-tuned. Vitreous zones were segmented into zone I (posterior vitreous (PV)), zone II (middle vitreous (MV)), and zone III (anterior vitreous (AV)).

Results: Control group mean VDI-N values were 0.767, 0.753, 0.548, and 0.842 for Zones I, II, III, and total vitreous respectively, compared to 0.775, 0.710, 0.596, and 0.775 in the uveitis group, showing significant differences ($p < 0.01$). Inter-grader reliability assessed by ICC and Bland-Altman plots revealed good to excellent agreement for VDI-N but variable for VDI-A, without statistical significance ($p > 0.05$).

Conclusion: High inter-grader agreement for VDI-N suggests reliable measurement, whereas variability in VDI-A due to factors like ILM hyperreflectivity indicates a need for further research. Future studies should increase grader numbers to improve VDI's diagnostic utility for vitreous inflammation in uveitis.

Ultrahigh-Resolution Optical Coherence Tomography for Vitreous Cell Differentiation in Uveitis Assisted by Artificial Intelligence

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Eric Suhler: None
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Purpose: This study explores an artificial intelligence (AI) assisted method to automatically identify and classify vitreous cells in uveitis using ultrahigh-resolution (UHR) optical coherence tomography (OCT). Having a non-invasive tool to quantify different types of vitreous cells can revolutionize uveitis care.

Methods: A 250-kHz retinal UHR-OCT prototype with 1.8 μm axial resolution (full-width-half-maximum in tissue) was used to image cells both in vitro and in vivo. Flow cytometry was employed to sort leukocytes separated from the human blood samples. Cell suspensions of neutrophils, lymphocytes, and monocytes were placed into cuvettes and imaged with OCT. A volumetric scan pattern (1 mm × 1 mm, 500 raster lines of 1000 axial scans each) was used. Custom-designed software algorithms were developed to automatically locate cells in the OCT volume as hyperreflective spots. For each cell, a 3-dimensional volume of 16×8×4 (axial × transverse × lateral) voxels, whose center matched the center of individual cells, were extracted from the OCT image. A lightweight convolutional neural network (CNN) model was developed to classify the types of inflammatory cells. In the clinical study, the posterior vitreous of patients with panuveitis or posterior uveitis and active inflammation was imaged with OCT. Vitreous cells were detected and analyzed using the same automated software, and the percentage

composition of the vitreous inflammatory cells was estimated.

Results: Four patients with posterior vitreous cells were imaged. One patient was diagnosed with Birdshot chorioretinopathy , one with chronic posterior uveitis, and the other two with chronic panuveitis. The CNN model detected predominantly lymphocytes (range 60.5% to 95.1%) in UHR-OCT images of the posterior vitreous for all three patients. These results aligned well with the clinical information.

Conclusions: AI-assisted UHR-OCT objectively quantified and classified posterior inflammatory cells, providing a valuable non-invasive diagnostic biomarker for aiding uveitis treatment decisions, understand the clinical course of diseases, and monitoring patients over time. Future studies with larger patient sample sizes and greater diversity of uveitis cases are needed to further investigate this method.

OCT-Based Evaluation of Vitreous Haze in the First-Line Antimetabolites as Steroid-Sparing Treatment Uveitis Trial

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Relevant Conflicts of Interest: None

Purpose: To evaluate the utility of spectral domain optical coherence tomography (SD-OCT) in the First-Line Antimetabolites as Steroid-Sparing Treatment (FAST) Uveitis Trial as surrogate for vitreous haze by using a relative vitreous signal intensity.

Methods: 213 eyes of 117 patients with SD-OCT images (Heidelberg Spectralis, Heidelberg Engineering, Germany) were included. OCT B-scan volumes were imported into validated OCTOR software and underwent semi-automated segmentation by an expert grader of the top of vitreous space, inner limiting membrane, and outer margin of the image to define two spaces:

(1) vitreous space and (2) rest of image (from ILM to the bottom of the image. For each OCT volume, 5 B-scans were used to calculate the relative vitreous signal intensity as a ratio of the vitreous space to the entire image.

Results: In the FAST Uveitis Trial, patients enrolled had the following Standardization of Uveitis Nomenclature (SUN) baseline haze grades were Grade 0 (n=101 eyes), 0.5+ (n=32), 1+ (n=45), 2+ (n=23), 3+ (n=5). Mean vitreous intensity at baseline was 0.464 and reduced to 0.398 (month 6) and 0.386 (month 12). A hybrid mixed model with random effects demonstrated that vitreous signal intensity was significantly positively correlated with SUN clinical grades ($p<0.001$).

Conclusion: In the FAST trial with follow-up over a period of 12 months, OCT-based vitreous signal intensity demonstrated possible utility as objective biomarker of vitreous haze.

RETINAL VASCULITIS

Pre-retinal Macrophage-Like Cells as Non-Invasive Biomarkers of Inflammation in Children with Uveitis

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Source(s) of Support: Knight Templar Eye Foundation
Relevant Conflicts of Interest: None

Purpose: Pre retinal macrophage-like cells (MLCs) can be visualized in vivo using en face optical coherence tomography (OCT) and has garnered attention as potential biomarkers of inflammation. This study aims to evaluate the feasibility of using these cells as non-invasive quantitative biomarkers of retinal vascular leakage in pediatric patients with uveitis.

Methods: In this retrospective study, we analyzed OCT-A scans of pediatric patients with uveitis and retinal vascular leakage on fluorescein angiography (FA) and healthy controls. Both groups underwent OCT-A and FA on the same day. Patient demographics and clinical findings were extracted from the electronic health records. Multiple OCT-A scans (5-10 per eye per location) were obtained from each eye, covering the fovea (3x3mm) and optic nerve head (ONH, 4.5x4.5mm). Using Fiji software, the 0 to 3µm slabs above the internal limiting membrane were registered, segmented, and averaged to identify and count the MLCs. Severity of leakage in each area (i.e. perifoveal and ONH) was graded (none, mild/moderate, and severe) by a masked grader. Additionally, area of fluorescein leakage on FA was quantified in the central 6mm Early Treatment Diabetic Retinopathy Study (ETDRS) circle using semiautomated methods.

Results: We included a total of 36 eyes from 20 consecutive pediatric patients (13 female, 65%; mean age 14.07 years, SD= 3.38) seen in the uveitis clinic. At baseline, 46.4% (n=15) and 41.4% (n=14) of the eyes showed evidence of leakage in the perifoveal

and ONH regions, respectively. MLC counts were significantly higher in eyes with severe leakage compared to those with mild/moderate or no leakage in both perifoveal area and ONH ($p<0.001$). A strong positive correlation was found between MLC counts in the perifoveal area and the area of fluorescein leakage (correlation coefficient: 0.78, $p<0.001$). No significant correlation was found between the degree of anterior chamber or vitreous cells and MLC numbers. During the 3 to 6 months follow-up, 41.2% (7/17) of the eyes showed decreased severity of perifoveal leakage on FA, whereas 17.6% (3/17) worsened. Changes in MLC counts were statistically significant across visits ($p=0.004$) and correlated with changes in fluorescein leakage ($p<0.001$).

Conclusions: Our study highlights the significant association between MLC numbers and retinal vascular leakage, indicating their potential utility as biomarkers for monitoring disease activity in pediatric uveitis. The dynamic changes in MLC counts corresponded with alterations in leakage severity, reinforcing their value in non-invasive disease monitoring.

Quantitative Analysis of Retinal Microvasculature Using Retinal Vascularity Index in Patients with Uveitis

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Relevant Conflicts of Interest: None

Purpose: This study investigates the differences in the Retinal Vascularity Index (RVI), including retinal arteriolar and venular diameters and arteriole-venule ratio (AVR), between uveitis patients and healthy controls.

Methods: Conducted at a tertiary eye center in Singapore, this cross-sectional case-control study included 28 uveitis patients with active inflammation and 40 healthy controls. Clinical data and multimodal imaging were obtained using a Zeiss Clarus 500 fundus camera. RVI parameters, such as arteriolar and venular diameters and AVR, were measured across three concentric zones around the optic disc (inner: 0-3 disc diameters, middle: 3-7 disc diameters, outer: 7-10 disc diameters) using specialized software. Differences in RVI were analyzed with the Mann-Whitney U test via Jamovi software.

Results: The mean age was 50.6 in the uveitis group and 48.9 in controls. Significant venular widening in the uveitis group was noted across all zones (inner: 4.2 vs 3.9 μm, $p=0.028$; middle: 3.8 vs 3.5 μm, $p=0.020$; outer: 3.3 vs 3.1 μm, $p=0.038$). Arteriolar diameters showed no significant differences. AVR was lower in the uveitis group in the inner (0.64 vs 0.70, $p=0.002$) and middle zones (0.64 vs 0.70, $p=0.006$).

Conclusion: RVI measurements reveal significant microvascular changes in uveitis, particularly venular dilatation, while arteriolar calibers remain similar to controls.

Validity of Spectral Domain OCT Angiography for Detection of Retinal Vasculitis

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Source(s) of Support: None
Relevant Conflicts of Interest: None

Objective: To evaluate the validity of Spectral-Domain OCT Angiography (SD OCTA) in the detection of small vessel retinal vasculitis (RV) at the posterior pole.

Methods: The subjects with and without retinal vasculitis on fundus fluorescein angiography (FFA) were identified among the clinic population and imaged with 8x8-mm SD-OCTA scans centered on the fovea on the same day. Three reviewers evaluated the FFA and composite en face flow/color thickness map, structure en face, and B scans of a customized segmentation on SD- OCTA in two separate sessions. The accuracy of the modified scans of SD OCTA for detection of RV was assessed by obtaining sensitivity, specificity, negative predictive value, and positive predictive values, together with 95% confidence intervals, where the gold standard was the consensus FFA result. Also, results from SD-OCTA were reviewed to introduce typical patterns suggesting retinal vasculitis.

Results: 18 eyes without retinal vasculitis and 34 eyes with retinal vasculitis were selected for evaluation. The sensitivity of SD-OCTA in identifying retinal vasculitis ranged from 76.5% to nearly 100%, depending on the reviewer. The specificity of SD-OCTA ranged from 61% to 78%. The positive predictive value of SD-OCTA ranged from 79% to 97%, and the negative predictive value of SD-OCTA ranged from 58% to 100%. Three main patterns were recognized on OCTA scans based on the presence of retina vessel staining, leakage, or both on FFA.

Conclusions: As a noninvasive method, SD-OCTA is a valid and sensitive imaging tool for the detection of small-vessel retinal vasculitis at the posterior pole.

RETINAL AND CHOROIDAL LESIONS

Optical Coherence Tomography-Based Choroidal Vascularity Index: Tracking Uveitis Progression Over Time

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Source(s) of Support: Grant from National Medical Research Council (NMRC) Singapore (Clinician Scientist-New Investigator Grant)
Relevant Conflicts of Interest: None

Purpose: To explore the longitudinal changes in the choroidal vascularity index (CVI) among uveitis patients with active inflammation, assessed at baseline and six months.

Methods: This prospective comparative study included 49 uveitis patients with varying subtypes and 49 healthy controls. Each participant underwent clinical assessments and multimodal imaging, including optical coherence tomography at baseline and six months. Both two-dimensional (2D) subfoveal and three-dimensional (3D) macular CVI were measured using established algorithms, with changes analyzed using an ANCOVA model.

Results: At baseline, 2D CVI was significantly lower in the uveitis group (62.4%) compared to controls (63.8%, p=0.007). The 3D CVI also trended lower in uveitis patients (62.0% vs 62.8%, p=0.109). Over six months, both 2D and 3D CVI increased in the uveitis group, though not significantly (p=0.055 and p=0.177, respectively). Patients with persistent active inflammation at six months exhibited lower baseline CVI than those who were clinically quiescent (p=0.027 for 2D, p=0.008 for 3D).

Conclusions: CVI correlates with both the diagnosis and prognosis of uveitis. Lower baseline CVI values are associated with ongoing inflammation at six months, suggesting CVI's potential as a valuable outcome measure in managing uveitis and in clinical trials.

Assessing and Following Patients with Birdshot Choroidopathy Using a Portable Handheld Electrodiagnostic Testing Device

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Source(s) of Support: None
Relevant Conflicts of Interest: None

Purpose: The flicker electroretinogram (ERG) is a sensitive indicator of retinal dysfunction in birdshot chorioretinopathy (BCR). In an earlier study, we explored recordings from a handheld device in BCR, comparing these with conventional standardised electrodiagnostic recordings in the same patients and with handheld ERGs from healthy individuals. In this study, we expand our patient numbers and have followed 25 BCR patients with serial comparative measurements.

Methods: Non-mydriatic flicker ERGs, using the handheld RETeval system (LKC Technologies), were recorded with skin electrodes using 32 Td.s/m2 flash stimuli with no background. Patients also underwent international standard flicker ERG recordings with conventional electrodes following mydriasis.

Results: 44 patients with BCR (mean age 62.8 ± 9.5 years) underwent recordings. Portable and standard ERG parameters correlated strongly ($r > 0.75$, $P < 0.01$). Limits of agreement for peak times were (n = 11; −3.4 to +6.9 ms [right eyes], −4.8 to +9.0 ms [left eyes]). In 25 patients, serial RETeval measurements accurately reflected changes in conventional flicker ERGs.

Conclusions: Portable ERGs correlated strongly with conventional recordings, suggesting that non-mydriatic flicker ERGs are an accurate, highly reproducible, and efficient modality to follow patients with BCR. Translational Relevance: Flicker ERGs, known to be useful in BCR, can be obtained rapidly with a portable device utilising skin electrodes and natural pupils to complement assessment in the clinical setting.

Relevant Publication: Waldie A, Hobby AE, Chow I Cornish EE et al. Electrophysiological assessment in birdshot choroidopathy: flicker electroretinograms recorded with a handheld device. Transl Vis Sci Technol. 2022;11(5):23 doi.org/10.1167/tvst.11.5.23

Objective AI Quantification of Longitudinal GVF Changes Secondary to Autoimmune and Inherited Retinal Diseases

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Source(s) of Support: None
Relevant Conflicts of Interest: None

Purpose: To develop an objective approach to monitor changes in the Goldmann visual field (GVF), which will be highly beneficial in evaluating inherited, autoimmune, and inflammatory ocular conditions, as well as monitoring the response to therapy.

Methods: Retrospective data were collected from 100 patients (180 eyes) with autoimmune retinopathy, retinal dystrophies, and uveitis, who had been followed up at a tertiary uveitis clinic. This dataset includes 1,000 GVF images taken across multiple visits. All personal and identifying information was redacted and the GVF exams were recorded on a blank template. With object and color detection techniques of the model, the size and intensity of the stimulus were automatically identified and plotted on the template. The distance of the plot from the grid center, measured in degrees, was recorded for each stimulus and displayed on a graph. Changes in responses to the stimuli were then calculated by registering longitudinal exams.

Results: The model was able to extract and generate digitalized version of the GVF in >97% of the cases. For certain GVF images where color extraction was inadequate or there was close proximity of certain colors, the results were unreliable, and these images were excluded from the study. The pilot results of our model demonstrate its ability in digitization of GVF data, measuring, and tracking changes over time, with potential for a wide range of future applications.

Conclusion: Extraction and digitalization of data from GVF is possible. Objective tools to quantify GVF can be employed to assess the visual changes in certain retinal pathologies.

Characterization of Retinal Microvascular Abnormalities in Birdshot Chorioretinopathy Using Optical Coherence Tomography Angiography

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Source(s) of Support: NIH Intramural Grant
Relevant Conflicts of Interest: None

Purpose: To characterize changes in the retinal microvasculature in eyes with birdshot chorioretinopathy (BCR) using optical coherence tomography angiography (OCTA).

Methods: A retrospective, observational, single center was performed and included twenty-eight patients (53 eyes) with BCR and 59 age-matched controls (110 eyes) were included in this study. En-face OCTA images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) of each eye were assessed for the presence of microvascular abnormalities and used to measure the vessel and foveal avascular zone (FAZ) areas. A longitudinal analysis was performed with a representative cohort of 23 BCR eyes (16 patients) at baseline and at a two-year timepoint. Main Outcome Measures: Whole-image vessel density (VD, %), extra-foveal avascular zone (extra-FAZ) VD (%), and FAZ area (%) were calculated and compared between control and BCR eyes. The frequency of microvascular abnormalities in BCR eyes was recorded.

Results: In the SCP, increased intercapillary space and capillary loops were common features present on OCTA images. Whole-image and extra-FAZ VD were lower in the BCR group compared with controls ($P < 0.0001$ [SCP and DCP]). FAZ area was enlarged in BCR eyes ($P = 0.0008$ [DCP]). Worsening best-corrected visual acuity was associated with a decrease in whole-image and extra-FAZ VD in the SCP ($P < 0.0001$ for both) and the DCP ($P < 0.005$ for both). Multivariable analysis, with vessel analysis parameters as outcomes, demonstrated that increasing age, increasing disease duration, lower central subfield thickness, and treatment-naïve eyes (compared to those on only biologics) were associated with a significant decrease in both DCP whole-image and extra-FAZ VD. Increasing disease duration was associated with a significant decrease in both SCP whole-image and extra-FAZ VD. Longitudinal analysis demonstrated no significant difference in any vessel analysis parameters except for an increase in DCP FAZ area.

Conclusion: Our results demonstrate a significant decrease in VD in BCR eyes and an association on multivariable analysis with disease duration. Quantifying VD in the retinal microvasculature may be a useful biomarker for monitoring disease severity and progression in BCR patients. Further studies with extended longitudinal follow-up are needed to characterize its utility in monitoring disease progression and treatment response.

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