

**American Uveitis Society Spring Meeting
Dedicated to Dr. Robert B. Nussenblatt, MD, MPH**

South Lake Union
750 Republican St., Seattle, WA 98109-8058

April 30, 2016

Program

5.00 PM Social Hour

6.00 PM Plenary Session: Imaging and the Eye

David R. Williams, PhD

Institute of Optics, University of Rochester

“Functional Imaging of the Living Retina at Cellular Resolution”

Richard F. Spaide, MD

Vitreous Retina Macula Consultants of New York

Department of Ophthalmology, NY School of Medicine

“Retinal Vascular Cystoid Macular Edema”

7.00 PM Business Meeting

7.30 PM Special Session:

Celebration of the Life of Robert B. Nussenblatt, MD, MPH

Led by James T. Rosenbaum, MD

Legacy Devers Eye Institute

Casey Eye Institute, Oregon Health & Science University

8.00 PM Free papers

**8.00 PM Maria Lopez, MD: “Multi-Photon Intravital Microscopy of Murine
Draining Lymph Nodes: a Powerful Tool to Study the Pathogenesis of
Ocular Inflammatory Diseases”**

**8.12 PM Thuy Doan, MD, PhD: “Illuminating Uveitis: Metagenomic Deep
Sequencing Common and Rare Pathogens”**

- 8.24 PM** **Ashvini Reddy, MD:** “Medical Malpractice in Uveitis: A Review of Clinical Entities and Outcomes”
- 8.36 PM** **Tiffany Lo, MBBS:** “Incidence of Uveitis in Fingolimod MS Treatment Trials”
- 8.48 PM** **Genevieve F. Oliver, FRANZCO:** “Use of Standardization of Uveitis Nomenclature for Reporting Clinical Data at 10 Years”
- 9.00 PM** **Maya Eiger-Moscovich, MD:** “Visual Outcome of Cystoid Macular Edema in Pediatric Non-Infectious Uveitis”
- 9.12 PM** **John H. Kempen, MD, PhD, MPH:** “Risk of Intraocular Pressure Elevation in Adults with Uveitis”
- 9.24 PM** **James Folk, MD:** “Late Onset Visual Field Loss in Patients with Pars Planitis and Retina Vasculitis”
- 9.36 PM** **Phoebe Lin, MD, PhD:** “Macular Circulation in Retinal Vasculitis Using OCT Angiography”
- 9.48 PM** **Karen R. Armbrust, MD:** “Gevokizumab in the Treatment of Autoimmune Non-Necrotizing Anterior Scleritis: Results of a Phase I/II Clinical Trial”
- 10.00** **Close of Meeting**

ABSTRACTS

Multi-Photon Intravital Microscopy of Murine Draining Lymph Nodes: a Powerful Tool to Study the Pathogenesis of Ocular Inflammatory Diseases

Author(s)

Lopez, Maria MD(1,3,4); Yamaguchi, Takefumi MD (4); Jamali, Arsia MD(1,2,3); Harris, Deshea MS(1,2,3), Hamrah, Pedram MD (1,2,3,4).

Affiliation(s)

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Abstract

PURPOSE: To develop a Multi-photon Intravital Microscopy (MP-IVM) murine model of the draining lymph nodes (dLNs) and to study the spatiotemporal characteristics of dendritic cells (DCs), in steady state and in inflammation (after corneal transplantation). To date, studies of these dLN have only been possible in ex vivo and in vitro studies.

METHODS: MP-IVM (Ultima Pro; Prairie Technologies) was used to image the submandibular dLNs. Anesthetized transgenic mice expressing green fluorescent protein for CD11c+ DCs were placed in a custom-build stage and the submandibular dLN was exposed. MP-IVM of the dLNs were performed on mice with normal corneas, as well as for corneas with isograft or allograft transplantation at 7, 14 and 21 days after surgery, during a period of at least 30 minutes. 4D imaging software was used to create 3D movies and analyse for DC kinetics.

RESULTS: MP-IVM imaging of dLNs demonstrated that DCs were distributed predominantly in the parafollicular cortex (T cell zone), but also in the subcapsular area, and sparsely in the follicles (B cell zone) in steady state as well after transplantation. While no significant increase in total host-derived DC density ($p>0.05$) was noted in isografts, allografts demonstrated a significant increase in host derived-DC density after 14 and 21 days compared to steady state ($p<0.05$). Allografts demonstrated increased velocity of host-derived DC in dLN as compared to controls ($p<0.001$). The meandering index significantly increased in corneal isografts ($p<0.01$) compared to normal controls, and further increased significantly in allografts ($p<0.0001$).

CONCLUSIONS: MP-IVM allows visualization of in vivo spatiotemporal kinetics and functionality of DCs in the murine submandibular dLN. MP-IVM will permit in vivo studies of the behavior of DCs and other immune cells in dLNs, providing an additional window into the corneal immune reflex arc and can be a powerful tool to study the pathogenesis of ocular inflammatory diseases.

Disclosure: None

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This research is NOT a clinical trial.

Illuminating Uveitis: Metagenomic Deep Sequencing Common and Rare Pathogens

Author(s)

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#These authors contributed equally to this work

Abstract

Purpose:

Diagnosing ocular infection is challenging due to the multitude of possible pathogens. Rapid advances in sequencing technology and bioinformatics have made the use of metagenomics increasingly feasible for a meaningful application of clinical diagnostics. In this study, we evaluated the utility of an hypothesis-free approach to identify ocular infections by performing unbiased metagenomic deep sequencing (MDS) on intraocular fluid of patients with inflammatory and non-inflammatory ocular disease.

Methods:

Intraocular fluid samples from 5 subjects with uveitis and 1 subject without uveitis were included in this study. RNA was extracted from 20-50 μ L of intraocular fluid and randomly amplified to double-stranded complementary DNA (cDNA). Depletion of Abundant Sequences by Hybridization (DASH), a novel molecular technique using the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-associated nuclease Cas9 in vitro, selectively depleted human mitochondrial cDNAs from the tagmented library, thus, enriching the MDS library for non-human (i.e., microbial) sequences. Samples were size-selected, pooled, and sequenced on an Illumina HiSeq 2500 instrument using 135 nucleotide (nt) paired-end sequencing. Sequences were analyzed using a rapid computational pipeline developed in-house.

Results:

MDS accurately detected viral (HSV-1), protozoan (*T. gondii*), and fungal (*C. neoformans*) infections in 3 positive control subjects and did not detect microbes other than known laboratory and environmental contaminants in subjects without intraocular infection. Furthermore, I will discuss the application of this technology to a 6th patient, who had a 16-year history of bilateral chronic anterior and intermediate uveitis, in which a single candidate pathogen was detected.

Conclusions:

Despite the small cohort, our results indicate that unbiased MDS can detect fungi, parasites, DNA and RNA viruses in minute volumes of intraocular fluid from patients with uveitis.

Disclosure: None

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This research is NOT a clinical trial.

Medical Malpractice in Uveitis: A Review of Clinical Entities and Outcomes

Author(s)

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Abstract

Purpose:

To guide risk management in uveitis.

Methods:

Retrospective review of malpractice verdicts, rulings, and settlements.

Results:

The WestLaw database was reviewed for lawsuits related to uveitis in the United States from 1930-2014. Twenty-five cases met inclusion criteria, and 48% of these were infectious. Overall, 64% of outcomes favored the defendant ophthalmologist. The most common diagnoses were viral retinitis (28%), iritis (12%), syphilis (8%), and toxoplasmosis (8%). Seven suits (28%) were resolved by settlement, with mean adjusted indemnities of \$724,302 (median, \$409,390; range, \$127,837 - 2,021,887). Two cases (8%) resulted in plaintiff verdict, with adjusted awards of \$1,399,800 and \$630,799.

Conclusions:

Despite being a rare diagnosis, viral retinitis (especially acute retinal necrosis) is the most common clinical entity associated with litigation in uveitis and should be considered early. Educating patients about potential adverse events, early testing for syphilis, and maintaining a positive relationship may also minimize risk.

Disclosure: None

Support: None

This research is NOT a clinical trial.

Incidence of Uveitis in Fingolimod MS Treatment Trials

Author(s)

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Affiliation(s)

1. Alfred Hospital Melbourne. 2. Eye Surgery Associates. 3. Centre for Eye Research Australia

Abstract

Purpose: To determine the incidence of uveitis in patients with multiple sclerosis (MS) treated with fingolimod, interferon or placebo.

Introduction: Uveitis and multiple sclerosis (MS) are related. There is an increased incidence of MS in patients diagnosed with MS. There is an increased incidence of uveitis in patients with MS with rates varying up to 0-1% in clinical studies and up to 11.5% in post-mortem studies. The immunology of MS and uveitis are similar and there are clear overlaps in the immunopathology seen in animal models. Fingolimod is a novel S-1-P receptor modulator. It has demonstrated ability to modulate MS and uveitis in animal models. More importantly it has a proven role in modulating human MS demonstrated in several seminal clinical trials. It has a dose related side effect of macular oedema seen in between 0.5 and 1% of patients in MS treatment trials. This has meant patients in human clinical trials of fingolimod have had close ophthalmic follow up. This allows us to accurately identify the incidence of uveitis in patients with MS treated with fingolimod or interferon or control.

Methods: Patients with relapsing remitting or chronic progressive MS were enrolled in 6 separate Novartis sponsored studies comparing oral fingolimod with placebo and uveitis. Patients had regular ocular examination and macular OCT. The incidence of uveitis was determined.

Results: Overall 4735 unique patients were treated in 6 different Novartis sponsored studies. The patients were treated with oral fingolimod at a dose of 0.5 or 1.25 mg or with interferon or with control. Overall 34/4735 (0.7%) developed uveitis. The rate of uveitis development was 0.29% in patients treated with fingolimod, 0.11% in patients treated with interferon, 0 in patients treated with placebo (P= 0.67). The pooled incidence of uveitis was 0.24% per year of follow up.

Conclusion: The rate of uveitis seen in these large closely followed groups of MS patients was around 0.7%. This may be an underestimate of the incidence of uveitis in the MS patients as patients thought to be at risk of macular oedema were excluded from the studies. There does not appear to be a reduced incidence of MS in patients treated with fingolimod.

Disclosure: AJH paid investigator for Novartis, paid Ad board for AbbVie. LL paid ad board for AbbVie. TL none

Support: AJH is a paid investigator for Novartis and was paid for his involvement in this study . TL none. LL none

This research IS a clinical trial and is registered at www.clinicaltrials.gov.

USE OF STANDARDIZATION OF UVEITIS NOMENCLATURE FOR REPORTING CLINICAL DATA AT TEN YEARS

Author(s)

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Affiliation(s)

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Abstract

PURPOSE

The “Standardization of Uveitis Nomenclature (SUN) for Reporting Clinical Data” was published in 2005, to promote communication between ophthalmologists managing patients with uveitis and to avoid ambiguity in the reporting of clinical data relating to uveitis (Jabs et al, *Am J Ophthalmol.* 2005; 140: 509-16). The criteria were developed by consensus across the international uveitis community, but adoption in the peer-reviewed ophthalmic literature has not been systematically evaluated to date.

METHODS

The PubMed database of the US National Library of Medicine of the National Institutes of Health was used to identify all peer-reviewed papers in the English language published between 1 October 2014 and 30 September 2015. Case reports, editorials and opinion pieces, reviews and meta-analyses, and animal studies were excluded. We collected data relating to journal, research group and study design. For each applicable study, we recorded use of the SUN anatomic classification, descriptors, inflammation grading, and outcomes and results reporting terminologies, using stringent definitions of compliance with the criteria. Statistical analyses to identify potential associations with use of SUN guidelines involved t-test for continuous explanatory variables (or rank sum test if data were skewed), and chi-square test for categorical explanatory variables.

RESULTS

A total of 771 peer-reviewed English language publications were identified by PubMed database search; 193 articles were reviewed. For 192 studies, the SUN anatomic classification was used in 102 (53%), and for 165 studies, the SUN descriptors of uveitis were used in 48 (29%). AC cell was graded by SUN recommendation in 39 of 58 studies (67%), and vitreous haze was graded by SUN recommendation in 20 of 39 studies (51%). Of 48 studies, 14 (29%) used SUN terminology to define activity outcomes, and of 98 studies, 47 (48%) used SUN terminology in reporting follow-up. Use of the SUN guidelines was not significantly associated with journal, author or study design items ($p > 0.05$). Interestingly, of the 64 studies that referenced the cited publication, 15 (23%) did not use the anatomic classification and 25 (46%) did not use the descriptors of uveitis.

CONCLUSION

Ten years after the SUN guidelines for reporting clinical data were published, these criteria are being used widely in studies published across journals, by diverse research groups and with multiple study designs. There are differences in the percentage adoption of specific components of the guidelines; anatomic classification, inflammation grading and follow-up reporting are more commonly used than some other components of SUN. Future analyses will consider additional determinants of the use of SUN guidelines.

Disclosure: NONE

Support: Australian Research Council (FT130101648)

This research is NOT a clinical trial.

Visual Outcome of Cystoid Macular Edema in Pediatric Non-Infectious Uveitis

Author(s)

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Abstract

Purpose: Cystoid macular edema (CME) is a major complication of non-infectious uveitis in children, often causing significant visual loss. CME is usually chronic, and may persist despite control of inflammation. This study investigated the visual outcome of CME in pediatric uveitis, with relation to treatment modalities.

Methods: In a retrospective study, the medical records of children treated for uveitis-related CME in four tertiary uveitis clinics in Israel and London between 2005-2015 were reviewed. Data included demographics, diagnosis, visual acuity, clinical and imaging findings and treatment given specifically for CME, and at 3,6,12 and 24 months thereafter.

Results: The study cohort included 28 eyes of 21 children (9 females and 12 male, mean age 8.2 ± 3.6 years). Median follow-up duration was 22 months (minimum four months). The most common diagnosis were pars planitis ($n=9$) and idiopathic anterior uveitis ($n=6$). Uveitis and CME were diagnosed simultaneously in 16 eyes (57%). Uveitis was active at CME diagnosis in 25 eyes (89%). Median time to resolution was 11 months (IQR 6-17), with complete resolution in 18 eyes (64%) by 24 months. Structural causes that limited CME resolution included epiretinal membrane, retinal vasculitis with neovascularization and vitreal traction. Baseline VA was $\leq 20/40$ in 7 eyes (25%), increased to 61.6% at 3 months ($p=0.007$), and remained stable thereafter. Treatment included corticosteroids (systemically and/or locally), immunosuppression and biologic therapies. No correlation was found between outcome and specific treatment strategy.

Conclusions: Prognosis of CME is favorable despite its chronic course. Larger cohorts are needed to define differences between treatment regimens.

Disclosure: None

Support: None

This research is NOT a clinical trial.

Risk of Intraocular Pressure Elevation in Adults with Uveitis

Author(s)

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Abstract

Purpose: To evaluate in adults the risk of and risk factors for intraocular pressure (IOP) elevation

Methods: Retrospective multicenter cohort study. The incidence IOP elevation were evaluated using cohort analysis at cohort entry and among those at free of each event at cohort entry respectively. When eyes received medical or surgical treatment, they were considered to have had an IOP elevation event. Potential predictive factors were evaluated using survival analysis with time-updated covariates as appropriate.

Results: Among 5,304 uveitic eyes of 3,324 patients, the incidence of IOP elevation to ≥ 30 mmHg was $\sim 10\%$ by one year, and continued to rise throughout follow-up to $\sim 30\%$ by ten years. Unilateral uveitis, poorer visual acuity at presentation, prior pars plana vitrectomy (not for retinal detachment), elevated IOP in the contralateral eye), time-updated presence of anterior chamber cells (dose-response pattern), and peripheral anterior synechiae were unmodifiable risk factors for incident IOP ≥ 30 mmHg. Treatment-related factors included use of oral (prednisone > 7.5 mg/day HR=1.85; prednisone ≤ 7.5 mg/day (HR=1.29) non-significant), topical (dose-response relationship, HR=1.62 for 1 drop of prednisolone acetate 1%/day or equivalent, HR=3.66 for 8 drops/day or higher), periocular (HR=4.01) corticosteroid injection in the last three months and fluocinolone acetonide implant ever (HR=9.7). Eyes with a history of hypotony has a lower incidence (HR=0.45). The strongest risk factors were contralateral elevation of IOP and more intensive corticosteroid delivery to the eye.

Conclusions: A vision-threatening degree of IOP elevation in ocular inflammatory diseases occurs frequently and continued to occur through at least ten years' follow-up. All forms of corticosteroids increase the risk of IOP elevation, in a dose-response relationship based on the dose delivered locally to the eye.

Disclosure: The author(s) have made the following disclosure(s): C. Stephen Foster: (equity owner) Eyegate, (consultant, lecturer) Allergan; (consultant, lecturer) Bausch & Lomb; (consultant) Sirion; (lecturer) Alcon; (lecturer) Inspire; (lecturer) Ista; (lecturer) Centocor; Douglas A. Jabs: (consultant) Roche; (consultant) Genzyme Corporation; (consultant) Novartis; (consultant) Allergan; (consultant) Glaxo Smith Kline; (consultant) Applied Genetic Technologies Corporation; (consultant) The Emmes Corporation; (consultant) The Johns Hopkins Dana Center for Preventive Ophthalmology; John H. Kempen: (consultant) Lux Biosciences; (consultant) Allergan; (consultant) Alcon; (consultant) Sanofi-Pasteur; (consultant) AbbVie; (consultant) Roche; James Rosenbaum: (equity owner) Amgen, (consultant) Abbott; (consultant), ESBATech, (consultant) Lux Biosciences, (consultant) Centocor, (consultant) Genentech.

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This research is NOT a clinical trial.

Late Onset Visual Field Loss in Patients with Pars Planitis and Retina Vasculitis

Author(s)

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Affiliation(s)

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Abstract

Purpose: To study the findings and clinical course of late onset severe visual field constriction in patients with retinal vasculitis.

Methods: The clinical records, retina images and visual fields were reviewed in two patients with pars planitis and one with retina vasculitis.

Results: The visual fields showed marked constriction in one eye of two patients and both eyes of the third. The field defects developed late (11,13,25) years after the patients were first seen. During the main follow-up period, all three patients had no or trace cells in the vitreous and anterior chamber and mild to no vascular leakage on FFA. The field defects occurred relatively suddenly and were associated with exacerbations of inflammation and worse leakage on FFA. OCT showed mainly outer retina damage in the areas corresponding to the field defects. The visual fields stabilized and the retina vascular leakage decreased after Retisert implantation in three eyes (one also had a vitrectomy) and Ozurdex injection every three months in the third patient. Central visual acuities remained 20/20, 20/25, 20/30 and 20/40) in the four affected eyes.

Conclusions: Marked visual field defects can occur suddenly after years of follow-up in patients with pars planitis and retina vasculitis whose inflammation appeared to be in fairly good control. Such patients need regular follow-up including at least yearly FFA and visual fields. It is unknown if any how retinal vascular leakage should be tolerated by treating physicians if there is otherwise no signs of inflammation. The vision loss in these patients appeared to be outer retinal in origin.

Disclosure: None

Support: Wynn Institute for Vision Research; Research to Prevent Blindness

This research is NOT a clinical trial.

Macular Circulation in Retinal Vasculitis Using OCT Angiography

Author(s)

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Affiliation(s)

Casey Eye Institute; Oregon Health & Science University

Abstract

Purpose

A feature of OCT angiography (OCTA) is its ability to provide a quantitative estimate of retinal blood flow by calculating vessel density. This study examines the macular blood flow, as measured by OCT angiography, in eyes with angiographically active retinal vasculitis compared to normal eyes.

Methods

Adult patients with retinal vasculitis were imaged with fluorescein angiography (FA) and OCTA with a commercially available 70 kHz Optovue SD-OCT using the split-spectrum amplitude decorrelation angiography algorithm (SSADA). A 3 x 3 mm angiogram centered at the fovea was obtained by projecting the flow signal internal to the retinal pigment epithelium in the en face orientation. Parafoveal vessel density was defined as percentage of pixels with detectable flow signal in a 1mm ring surrounding the fovea. The choriocapillaris vessel density was calculated as a percentage of pixels with detectable flow signal within 10 microns external to the RPE in the 3x3mm area.

Results:

5 patients (7 eyes) with a history of angiographically active retinal vasculitis were included in the study. Their diagnoses included lupus retinal vasculitis with choroiditis, Behçet's disease, TINU with retinal vasculitis, sarcoidosis, and idiopathic retinal vasculitis. Data from 11 normal eyes were drawn from a previously compiled database. The average retinal vessel density in normal eyes was significantly higher than that of retinal vasculitis patients ($p=0.006$). The choriocapillaris vessel densities were also significantly higher in normal subjects compared to retinal vasculitis patients. Additionally, treatment response was able to be quantitated in the patient with lupus vasculitis using OCTA.

Conclusions

This technique shows promise as a possible biomarker for determining disease activity, and gauging treatment response in patients with retinal vasculitis.

Disclosure: No pertinent financial relationships

Support: None

This research is NOT a clinical trial.

gevokizumab in the treatment of autoimmune non-necrotizing anterior scleritis: Results of a phase I/II clinical trial

Author(s)

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Affiliation(s)

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Abstract

PURPOSE: To evaluate the safety and potential efficacy of gevokizumab, an anti-interleukin 1 β (IL-1 β) monoclonal antibody, in the treatment of active, non-infectious, non-necrotizing, anterior scleritis.

DESIGN: Phase 1/2, open label, non-randomized, prospective, single-arm, pilot trial

METHODS: Eight patients with active, non-infectious, non-necrotizing, anterior scleritis with a scleral inflammatory grade of +1 in at least one eye were enrolled. In one patient, both eyes were enrolled, for a total of nine eyes. Patients received one subcutaneous injection of 60 mg gevokizumab at baseline and then every four weeks for 12 weeks. The primary outcome was at least a 2-step reduction or reduction to grade 0 in scleral inflammation on a 0 to +4 scale according to a standardized photographic scleritis grading system by 16 weeks in the study eye compared to baseline. Participants who met the primary outcome were eligible to continue in the study for up to 52 weeks. Secondary outcomes included changes in visual acuity, intraocular pressure, and trends in scleral grading.

RESULTS: Nine eyes from eight patients with scleral inflammation ranging from +1 to +3 were enrolled (four eyes with +1, one eye with +2, and four eyes with +3). Seven eyes from seven patients met the primary outcome within a median time of two weeks following the first gevokizumab injection. No definitive changes in visual acuity or IOP were identified. There were no serious adverse events related to the study drug. A total of 43 adverse effects were reported with 93% described as mild, 95% as non-ocular, and only 14% deemed possibly caused by the investigational treatment.

CONCLUSIONS: The results of this small study suggest that blockage of IL-1 β using gevokizumab may be beneficial in treating active scleritis and that gevokizumab is well-tolerated. Larger randomized trials are warranted to assess the true efficacy of gevokizumab in the treatment of non-necrotizing anterior scleritis.

Disclosure: None

Support: This research was supported by the Intramural Research Program of the NIH, NEI. The study medication was provided by Xoma Corporation (Berkeley, CA).

This research IS a clinical trial and is registered at www.clinicaltrials.gov.