

AMERICAN  UVEITIS SOCIETY

Annual Meeting

AAO 2008

Sunday, November 9, 2008
Marriott Marquis
Atlanta, Georgia

Schedule – American Uveitis Society – Sunday November 9, 2008

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|--------------------|---|
| 7:30 pm – 8:00 pm | Cocktails/Social Hour |
| 8:00 pm | Welcome |
| 8:05 – 8:25 pm | <i>Basic Science Literature Review</i> – Russell Van Gelder, MD |
| 8:25 – 8:45 pm | <i>Clinical Science Literature Review</i> – Russell Van Gelder, MD |
| 8:45 pm – 9:00 pm | Business Meeting & Break |
| 9:00 pm – 10:30 pm | Research Presentations
(7 minutes each with 3 minutes for Questions) |
- *Useful Imaging Techniques in the Diagnosis and Management of patients with Anterior Segment Pathology* – Roxana Ursea MD
 - *Cirrus (Spectral Domain) Optical Coherence Tomography for imaging of the posterior segment in patients with uveitis* – Sofia Androudi MD, PhD
 - *Case Presentation of Placoid Chorioretinitis and Literature Review* – Rachael S Horn, MD
 - *Durezol™ compared to Pred Forte® in the treatment of endogenous anterior uveitis* – Thomas Flynn, MD
 - *Dexamethasone in an Intravitreal Drug Delivery System* - Michael R. Robinson, MD
 - *Methotrexate for Ocular inflammatory diseases* – Sapna Gangaputra, MD, MPH
 - *Demographic Characteristics from the LUMINATE Clinical Trials Exploring LX211, a Next Generation Calcineurin Inhibitor for the Treatment of Non-infectious Uveitis* - Quan Dong Nguyen, MD
 - *Risk of cataract development among children with juvenile idiopathic arthritis (JIA)-associated uveitis* – Jennifer Thorne, MD, PhD
 - *Azathioprine Monotherapy and SITE Cohort Study* - Sirichai Pasadhika, MD
 - *Intraocular Penetration of Infliximab in patients receiving systemic therapy for uveitis* – Shelley Lee MD

Title:

Useful imaging techniques in the diagnosis and management of patients with anterior segment pathology: ultrasound biomicroscopy and anterior segment Optical Coherence Tomography

Author:

Roxana Ursea, MD

Purpose:

Ocular pathology affecting the anterior segment can present diagnostic problems because it often involves structures that are not readily accessible by routine examination methods. Our goal was to assess and compare the utility of ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (OCT) in the evaluation and management of patients with ocular pathology involving the anterior segment of the eye.

Methods:

Retrospective review of 34 eyes with various conditions involving the anterior segment, examined with high-resolution ultrasonography (Sonomed, Inc, Lake Success, NY) and anterior segment OCT (Carl Zeiss Meditec Inc., CA) over a period of 12 months. The findings were determined and the clinical relevance of UBM and anterior segment OCT information was analyzed.

Results:

Abnormalities were found in 29 eyes of patients with the following etiologic diagnoses: anterior scleritis, intermediate uveitis, traumatic hyphema, foreign body, iris or ciliary body mass and intraocular lens. Indications for the UBM were: visualization of anterior chamber structures, visualization of posterior iris or ciliary body, assessment of intraocular lens position, pre-operative assessment in eyes with hypotony or trauma and for follow-up of documented abnormalities. Indications for anterior segment OCT were: assessment of the angle, measurement of corneal thickness, visualization of anterior iris, preoperative assessment.

Conclusions:

The combination of UBM and anterior segment OCT offers a complete assessment of the anterior segment. Both are sensitive imaging techniques that provide excellent diagnostic clues in patients with anterior segment involvement. UBM is invaluable in accurately visualizing the posterior iris and ciliary body region. In the majority of cases the high-resolution imaging techniques confirmed the clinical diagnosis and was useful in the follow up of patients and surgery planning.

Cirrus (Spectral Domain) Optical Coherence Tomography for imaging of the posterior segment in patients with uveitis

*Sofia Androudi, MD, PhD, Christos Kalogeropoulos, MD, PhD, Periklis Brazitikos, MD
Aristotle University Eye Clinic, Thessaloniki, Greece, University Eye Clinic of Ioannina, Greece*

Purpose:

High-definition (HD) spectral-domain optical coherence tomography [SD-OCT] offers major advantages in imaging by providing high-resolution, cross-sectional images of the retina; it can acquire three-dimensional (3D) scans at a high speed and provides excellent point-to-point registration. The purpose of our study was to evaluate high-definition SD-OCT (Cirrus HD-OCT; Carl Zeiss) for imaging of the posterior segment in patients with uveitis.

Methods:

Twenty consecutive patients with anterior or posterior uveitis of various causes and anterior chamber cells or vitreous haze of 2+ or worse had their media opacity graded and OCT scans both on TD-OCT (Stratus) and SD-OCT (Cirrus). All scans were performed twice in both OCT machines and all patients underwent slit lamp and posterior segment photography to accurately evaluate the media clarity and vitreous haze. The SD-OCT scan protocol was macular cube and 5-line raster. Information obtained from SD- OCT scans was compared to that obtained from TD- OCT scans.

Results:

In all scans performed with SD- OCT, the strength of the signal was within the acceptable range (>5/10). Cases with marginal acceptable signal strength (4 and 5) with SD- OCT, showed a very poor scan quality with TD- OCT that deterred any safe interpretation. Additional information on SD- OCT could be obtained in twelve (60%) of the 20 eyes examined (epiretinal membrane morphology, adhesion of vitreous in the macula, areas of retinal atrophy, minimal cysts in the macula).

Conclusions:

SD- OCT in uveitis can provide acceptable scan quality in cases with poor media clarity and provides significantly more clinical information compared with the standard TD-OCT.

Relentless Placoid Chorioretinitis

We present a case of a 30 year old female with relentless placoid chorioretinitis, or ampingous chorioretinitis, and a review of the literature.

Our patient presented with a one month history of flashes and floaters in the left eye. Past medical history was significant for cholecystectomy, recurrent pneumonia, anxiety and depression, borderline diabetes and a history of chicken pox.

On initial examination, VA was 20/20 OU. Anterior segment exam revealed 2+ cells in the anterior chamber OS and 1+ anterior vitreous cells. Retinal examination was significant for sectoral peripheral confluent retinochoroiditis, with associated intraretinal hemorrhage OS. The retina in the right eye was normal.

Initial laboratory studies were performed to rule out infectious and inflammatory etiologies. Based on clinical appearance, the initial leading diagnostic etiology was acute retinal necrosis (ARN) secondary to herpesvirus. An anterior chamber paracentesis was performed for viral PCR, which was negative. Initial treatment was directed toward viral retinitis and consisted of intravitreal foscarnet, Valtrex and Bactrim (for possible toxoplasmosis). In the midst of evaluation, she developed a rash in the trigeminal distribution with accompanying ocular pain concerning for HSV; skin biopsy was performed which was also negative for herpes. After laboratory evaluation excluded an infectious etiology, systemic high-dose prednisone was started under antiviral cover. Due to progression of retinitis, a diagnostic vitrectomy was performed nine days after presentation with laser demarcation and repeat intravitreal foscarnet. The vitreous sample was negative for herpesvirus PCR. Given a clinical response to high dose systemic prednisone, our patient was continued on systemic steroid treatment under antiviral cover. As systemic prednisone was tapered, the patient developed recurrence of symptoms which did respond to steroid sparing immunomodulation. Disease activity and vision have remained stable over the past 8 months until a most recent reactivation with systemic steroid taper.

The clinical appearance is most consistent with relentless placoid chorioretinitis with serial photographs demonstrating a progressive course. The optimal management of this uncommon entity is unknown. We present this case with a review of the current literature and a discussion of further treatment options.

Durezol™ compared to Pred Forte® in the treatment of endogenous anterior uveitis

Thomas Flynn, MD
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Purpose:

Evaluate the efficacy and safety of Durezol™ (difluprednate ophthalmic emulsion, 0.05%) dosed four times daily (QID) for 14 days, versus Pred Forte® (prednisolone acetate suspension), 1%, dosed 8 times daily for 14 days in treating endogenous anterior uveitis.

Methods:

A randomized, multicenter, double-masked trial was conducted in 90 subjects, comparing Durezol QID to Pred Forte eight times a day. Both groups were treated with the test agent for 14 days, followed by 2 weeks of tapering at half the dose, and two weeks of follow-up. Subjects aged 2 or older with endogenous anterior uveitis in at least 1 eye, plus >10 cells and a flare score of ≥ 2 in the anterior chamber (AC) of that same eye were eligible for participation. Subjects were randomized in a 1:1 ratio to receive either Durezol or Pred Forte.

Results:

At Day 14 the Durezol group achieved a mean cell grade reduction of 2.1 vs 1.9 in the Pred Forte group. A greater percentage of Durezol patients had an AC cell grade of 0 (≤ 1 cell) than the Pred Forte at Day 14 (69% vs 62%, respectively). By Day 7, Durezol subjects had a reduction in the mean pain score of 71% versus 64% in the Pred Forte group. In the Pred Forte group, 12.5% of patients were withdrawn due to lack of efficacy or adverse events related to worsening of symptoms; no Durezol patients were withdrawn for these reasons. Only two patients in each treatment arm experienced a criterion increase in intraocular pressure (defined as a pressure of ≥ 21 mmHg and a change from baseline ≥ 10 mmHg at the same visit).

Conclusion:

Durezol administered QID is as effective as Pred Forte dosed eight times a day in treating uveitis. Durezol was also safe and well tolerated.

Dexamethasone in an Intravitreal Drug Delivery System Reduces Levels of Inflammatory Mediators in a Model of Experimental Anterior/ Intermediate Uveitis

*J. Burke, C. Ghosn, Y. Li, W. Orilla, T. Lin, L. Wheeler, S.M. Whitcup, M.R. Robinson
Biological Sciences, Allergan, Inc, Irvine, CA.*

Purpose:

Intravitreal dosing of corticosteroids can improve drug delivery to the vitreous and retina and limit the side effects associated with oral dosing. The purpose of this study was to evaluate the effect of a sustained-release biodegradable intravitreal dexamethasone posterior segment drug delivery system (DEX PS DDS) on cytokines and chemokines that are up-regulated in experimental uveitis in rabbits.

Methods:

Uveitis was induced by an intracameral injection of 20µg Mycobacterium Tuberculosis (Mbt) in one eye of 18 rabbits pre-immunized 20 days earlier with 2 subcutaneous doses of 10mg Mbt. Four days after disease induction, animals had either a 22-gauge sham injection (n=6) or intravitreal DEX PS DDS 700 µg (n=12). At 3 weeks, anterior chamber cells and corneal thickness were assessed with a slit lamp (grading scale 0-4+), and the Visante anterior segment OCT, respectively. The iris ciliary body (ICB) was also assayed for 89 chemokines/cytokines using the Luminex assay. Groups were compared using unpaired Student's t-tests.

Results:

At 3 weeks, DEX PS DDS significantly reduced anterior chamber inflammatory cell scores: mean (\pm SD) cell scores were 1.9 ± 0.3 for DEX PS DDS and 4.0 ± 0 for sham ($p < 0.05$). Corneal thickness was significantly lower in DEX PS DDS-treated animals (406 ± 111 µm) compared with sham (802 ± 73 µm; $p < 0.05$). Normal corneal thickness was 353 ± 14 µm. Ten chemokines/cytokines were up-regulated 3-fold or greater in the sham group ICB compared with naïve eyes: BDNF, CD40, IL-1 beta, IL-8, MIP-1alpha, MIP-1beta, MMP-2, RANTES, VCAM-1, and VEGF. Increases ranged from 3-fold for MIP-1 alpha ($< 2.6 \pm 0$ pg/ml to 7.2 ± 3.1 pg/ml) to 1488-fold for RANTES (1.8 ± 1.9 pg/ml to 2.7 ± 0.74 ng/ml). DEX PS DDS reduced the ICB levels of all 10 mediators by 33% - 88%.

Conclusion:

Intravitreal DEX PS DDS significantly reduced intraocular inflammation in an experimental model of anterior/ intermediate uveitis.

Title: Methotrexate for ocular inflammatory diseases.

Authors:

Sapna Gangaputra MD, MPH,^{1,2} Craig W. Newcomb, MS,^{4,5} Teresa L. Liesegang, COT, CRC,⁷ R. Oktay Kaçmaz, MD, MPH,⁹ Douglas A. Jabs, MD, MBA,^{2,3,10} Grace A. Levy-Clarke, MD,^{11,12} Robert B. Nussenblatt, MD, MPH,¹² James T. Rosenbaum, MD,^{7,8} Eric B. Suhler, MD, MPH,^{7,13} Jennifer E. Thorne, MD, PhD,^{2,3} C. Stephen Foster, MD,^{9,14} and John H. Kempen, MD, PhD⁴⁻⁶ for the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study.

Affiliations:

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Purpose:

To evaluate outcomes of methotrexate as a single immunosuppressive agent for non-infectious ocular inflammation.

Methods:

Participants were identified from the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study database. Demographic and clinical characteristics, including dosage and route of administration of methotrexate and the main outcome measures, were obtained for every eye of every patient at every visit by retrospective medical record review.

Results:

Of the 534 patients (919 eyes) treated with methotrexate, 24%, 17.6%, 26.4%, 15.9%, 11.2%, and 4.7% respectively had anterior uveitis, intermediate uveitis, posterior or panuveitis, scleritis, ocular mucous membrane pemphigoid, and other forms of ocular inflammation. In these groups, complete suppression of inflammation (success over ≥ 2 visits spanning ≥ 28 days) was achieved in ≤ 6 months in 54.3%, 16.9%, 21.8%, 35.8%, 38.3%, and 76.7% respectively. Corticosteroid-sparing success (complete control of inflammation with prednisone dose of 10 mg/day or less over ≥ 2 visits spanning ≥ 28 days) was achieved within 6 months among 45.1%, 15.5%, 12.9%, 26.1%, 35.5%, and 47.8% respectively. Methotrexate was discontinued within ≤ 1 year by 42% of patients, most commonly due to side effects (83 patients, 16%) which typically were reversible with dose reduction/discontinuation.

Conclusions:

Our data suggest that methotrexate as a single immunosuppressive agent, on average, is reasonably effective for management of anterior uveitis, moderately effective for scleritis and mucous membrane pemphigoid, and less effective for intermediate uveitis and posterior or panuveitis. Methotrexate was well tolerated by the large majority of patients, and appears to convey little risk of serious, long-term side effects.

Demographic Characteristics from the LUMINATE Clinical Trials Exploring LX211, a Next Generation Calcineurin Inhibitor for the Treatment of Non-infectious Uveitis

Quan Dong Nguyen for the LUMINATE (LX211 Uveitis Multicenter Investigation of a New Approach to Treatment) Study Group

Introduction:

LX211 is the oral formulation of a novel, next-generation calcineurin inhibitor (voclosporin). The LUMINATE studies have been designed as pivotal clinical trials to evaluate the safety and efficacy of LX211 as a corticosteroid-sparing agent for the management of non-infectious uveitis.

Methods:

Three global, prospective, double-masked, parallel-group, dose-ranging, placebo-controlled, randomized multi-center studies comprise the LUMINATE Program, which is currently in progress in 57 sites across North America, Europe, and India. Study LX211-01-UV evaluates 218 patients with active predominantly posterior manifestations. Study LX211-03-UV evaluates 108 patients with active predominantly anterior manifestations. Study LX211-02-UV evaluates 232 patients whose disease is controlled and will evaluate the safety and efficacy of LX211 in sparing systemic corticosteroid and, if applicable, in replacing a poorly-tolerated corticosteroid-sparing agent.

Results:

Pooled masked data from the studies to date indicate that in Study LX211-01 the distribution of patient anatomic diagnoses is: panuveitis (49.5%), intermediate uveitis (29.2%), anterior + intermediate uveitis (11.4%) and posterior uveitis (12.9%). The mean age of subjects in LX211-01 is 41.8 years (13.8 SD) with a predominance of female subjects (60.4%). Study LX211-02 includes subjects with panuveitis (40.8%), intermediate uveitis (27.2%), anterior + intermediate uveitis (11.4%), and posterior uveitis (20.6%). The subject mean age is 42.8 years (13.9 SD) with a predominance of female (63.9%) subjects. In Study LX211-03, the distribution of patient anatomic diagnoses is notable for a majority of randomized subjects diagnosed with anterior uveitis (50.4%) followed by panuveitis (31.8%) and intermediate uveitis (27.2%). The mean age of subjects in LX211-03 is 36.7 years (12.9 SD); study LX211-03 is also predominantly female (62.1%).

Conclusion:

The LUMINATE Program is the first randomized placebo-controlled set of trials ever conducted to evaluate the safety and efficacy of a corticosteroid-sparing immunomodulatory agent in different types of sight-threatening non-infectious uveitis. The wide range of disease types may permit their results to be applied broadly across disease categories and patient populations.

Title:

Risk of cataract development among children with juvenile idiopathic arthritis (JIA)-associated chronic anterior uveitis treated with topical corticosteroids

Authors:

Jennifer E. Thorne, MD, PhD,^{1,2} Fasika Woreta, MD, MPH,¹ James P. Dunn, MD,¹ Douglas A. Jabs, MD, MBA^{2,3}

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ABSTRACT:**Purpose:**

To report any increased risk of cataract development among patients treated with variable doses of topical corticosteroids among children with juvenile idiopathic arthritis (JIA)-associated uveitis.

Design:

Retrospective cohort study

Methods:

Setting: Single-center, academic practice. *Study population:* 75 patients with JIA-associated uveitis observed from July 1984 through August 2005. *Procedures:* Clinical data on these patients were analyzed. *Main outcomes measures:* Incidence of new-onset cataract development.

Results:

Over a median follow-up of 3 years (range: 6 months to 15 years), the incidence of new-onset cataract was 0.05/eye-year (EY, 95% confidence interval [CI]: 0.02//EY, 0.09/EY). Of the 60 eyes in 40 patients who received chronic topical corticosteroid therapy, the incidence of cataract development was 0.01/EY for eyes treated with 3 drops daily or less and 0.16/EY $P = 0.0006$ for log rank test) for eyes treated with >3 drops daily. Among eyes of patients receiving ≤ 2 drops daily, the incidence of cataract was zero. After controlling for duration of uveitis, presence of active uveitis and concomitant use of other forms of corticosteroids (i.e., oral prednisone) in a time-dependent fashion, treatment with ≤ 3 drops daily of topical corticosteroid was associated with a 87% lower risk of cataract development compared to those eyes treated with >3 drops daily (relative risk = 0.13, 95% CI: 0.02, 0.69, $P = 0.017$).

Conclusions:

The incidence of cataract development in our cohort was lower than that observed in adult patients with uveitis (~0.08-0.10/EY). Chronic topical corticosteroid use at doses of 3 drops daily or less was associated with a small risk of cataract development during the period of observation.

**Azathioprine Monotherapy for Non-infectious Ocular Inflammatory Diseases:
Experience from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE)
Cohort Study**

Sirichai Pasadhika, MD, John H. Kempen, MD, PhD, Craig W. Newcomb, MS, Teresa Liesegang, COT, CRC, Siddharth S. Pujari, MD, James T. Rosenbaum, MD, Jennifer E. Thorne, MD, PhD, C. Stephen Foster, MD, Douglas A. Jabs, MD, MBA, Grace A. Levy-Clarke, MD, Robert B. Nussenblatt, MD, MPH, and Eric B. Suhler, MD, MPH, for the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study.

Purpose:

To evaluate treatment outcomes with azathioprine as a single steroid-sparing immunosuppressive agent in patients with non-infectious ocular inflammatory diseases.

Design:

Retrospective cohort study.

Participants:

209 consecutive patients with non-infectious ocular inflammation treated with azathioprine monotherapy at the tertiary uveitis services contributing to the SITE database.

Methods:

Medical records of participants were reviewed. Response to therapy, dose of prednisone, history of previous immunosuppressive drugs, and reasons for discontinuation of azathioprine were recorded.

Main outcome measures:

The ability to improve global activity of inflammation, ability to taper corticosteroids to a dose of ≤ 10 mg daily, and incidence of treatment-related side effects leading to discontinuation of treatment.

Results:

Of the 209 patients (376 eyes) treated with azathioprine monotherapy, 67% had uveitis, 14% had scleritis, 16% had mucous membrane pemphigoid, and 3% had other inflammatory diseases. Of 140 patients (248 eyes) with uveitis, 16% had anterior, 27% were intermediate, and 56% were posterior or panuveitis. Survival analysis demonstrated 39% (95%CI, 31-48%) of patients with active disease experienced an improvement of inflammation to 'inactive' or 'slightly active' in their global activity scale, and 24% (95%CI, 18-32%) could taper corticosteroids to ≤ 10 mg daily, within 6 months of initiating azathioprine therapy. Over the median follow-up of 210 days (interquartile range, 63-608), 133 patients (64%) discontinued azathioprine: 23% due to side effects, 15% due to failure to control inflammation, 11% due to disease remission, and 15% due to unspecified causes. Azathioprine was discontinued due to failure to control inflammation at a rate of 0.10 per person-years (PY) and due to adverse effects at a rate of 0.15 /PY. The most common side effect leading to discontinuation was gastrointestinal upset, with an occurrence rate of 0.06/PY.

Conclusions: Azathioprine may be tolerable and effective as a single steroid-sparing immunosuppressive agent for the treatment of non-infectious ocular inflammatory diseases.

Intraocular Penetration of Infliximab in Patients Receiving Systemic Therapy for Uveitis Lee ST, Rosenbaum JT, Suhler EB

Purpose:

To assess the intraocular penetration of infliximab in patients undergoing systemic therapy for noninfectious uveitis.

Design:

Case series

Method:

We reviewed the records of 4 patients receiving intravenous infliximab therapy for refractory noninfectious uveitis, uncontrolled with more traditional immunomodulatory therapy as part of our prospective clinical trial and sampled the aqueous and/or vitreous of patients who underwent cataract surgery and/or vitrectomy during the course of infliximab therapy. All four patients were felt clinically to have well controlled inflammation at the time of surgery.

Results:

Two of four patients had detectable concentrations of infliximab present in the aqueous (203.87 ng/mL, 110.68 ng/mL). These patients underwent surgery 5 and 6 weeks after infliximab infusions of 7 and 5 mg/kg, respectively. Of the two without detectable aqueous levels (<100.0 ng/mL) of infliximab, one had detectable infliximab concentrations in the vitreous (avg 143.01 ng/mL) which was obtained contemporaneously, approximately 10 weeks after her last infliximab infusion.

Conclusions:

To our knowledge this is the first report confirming the intraocular penetration of infliximab in patients undergoing systemic infliximab therapy. In most cases, detectable infliximab was present in the eye from 5 to 10 weeks after infliximab administration, but two of four cases with clinical quiescence did not have detectable aqueous levels. The concentrations we have identified, taken in accordance with Perez-Guijo et. al. findings of TNF-alpha levels of approximately 15 pg/mL in the aqueous humor (Curr Med Res Opin 2004), imply sufficient intraocular concentration of infliximab for a local effect, suggesting that both local and systemic effects of infliximab may be important in its anti-inflammatory effects for ocular disease. Further study is indicated to better define systemic and local factors contributing to immunosuppressive control of intraocular inflammation, which may better direct continuing efforts at optimizing directed care of uveitic diseases.