Uveitis literature 2014: the year in review

Russell N. Van Gelder, MD, PhD
Department of Ophthalmology
University of Washington
Seattle, WA
Disclosures

• RVG serves as
  – Associate Editor of IOVS
  – Editorial Board Member of *Ophthalmology*
  – Editorial Board Member of Ocular Inflammation and Immunology

• RVG received research funding in 2014 from:
  – National Eye Institute
  – Research to Prevent Blindness
  – Alcon Research Labs/Novartis
  – NovaBay
  – Theravance
Purpose

To bring papers of potential significance and interest to the attention of the AUS membership and guests
Methods

• Literature search for ‘uveitis’ or ‘ocular inflammation’ on PubMed

• Limited to English language and added to database in the last year (11/1/13 to 10/31/14)

• Selected ~ 30 papers to discuss briefly based on impact in understanding or managing ocular inflammatory disease
Caveats

• This is a necessarily subjective process
• Less than 2% of the literature can be featured
• All omissions are exclusively my fault and should not be taken personally
Uveitis literature 2013-14

• 1354 papers in English
• 552 human
• 157 reviews
• 50 clinical trials
Basic Science

“What’s the opposite of ‘Eureka’?”
ANIMAL MODELS

Spontaneous Development of Autoimmune Uveitis Is CCR2 Dependent

YuTing Feeling Chen,* Delu Zhou,* Todd Metzger,† Marianne Gallup,* Marion Jeanne,* Douglas B. Gould,† Mark S. Anderson,* and Nancy A. McNamara*†‡

From the Francis I. Proctor Foundation,* the Diabetes Center,* and the Departments of Ophthalmology† and Anatomy‡, University of California, San Francisco, California, and the School of Optometry* and the Vision Science Program,† University of California, Berkeley, California

- AIRE mice get spontaneous panuveitis due to loss of self-tolerance
- When crossed into C-C chemokine receptor 2 KO mice, uveitis is minimal
- CCR2 function was in bone-marrow derived cells
- Suggests CCR2 may be an excellent target for uveitis drugs
- HMGB1 is a chromatin protein secreted by activated mononuclear cells
- Activates TLR-4 via MyD88
- Accumulates in EAU
- Neutralizing antibodies reduce EAU)
- MyD88-/- mice show no EAU pathology (Caspi ‘05) but TLR knockouts susceptible -> HMGB1 effector?
EC0746 is a rationally designed drug conjugate of a folic acid ligand and an analog of aminopterin.

- Taken up by activated macrophages
- Treated rats with S-Antigen peptide EAU 8 days after initiation of disease with four subcutaneous doses (every other day)
- Near complete amelioration of EAU observed
- Could be competed away with folic acid receptor competitor
Protective efficacy of *Toxoplasma gondii* calcium-dependent protein kinase 1 (TgCDPK1) adjuvated with recombinant IL-15 and IL-21 against experimental toxoplasmosis in mice

Jia Chen¹, Zhong-Yuan Li¹,², Si-Yang Huang¹*, Eskild Petersen³, Hui-Qun Song¹, Dong-Hui Zhou¹ and Xing-Quan Zhu¹,²*

- Immunized mice with a DNA vaccine to *T. gondii* calcium-dependent protein kinase
- Used IL-15/21 expressing adjuvant
- Marked improvement in survival to lethal load of toxoplasmosis
- Reduced cyst load in animals
Earth people.
We come in peace. Let's enjoy fun. We are not eating you quickly.

Darn that google translate.
Toxoplasma Serotype Is Associated With Development of Ocular Toxoplasmosis

Leila Shobab,1,a Uwe Pleyer,1,a Joerdis Johnsen,3 Sylvia Metzner,3 Erick R. James,5 N. Torun,3 Michael P. Fay,2 Oliver Liesenfeld,4 and Michael E. Grigg1,5

1Laboratory of Parasitic Diseases, and 2Biostatistics Research Branch, NIAID, National Institutes of Health, Bethesda, Maryland; 3Department of Ophthalmology, and 4Institute of Microbiology and Hygiene, Charité–University Medicine Berlin, Germany; and 5Department of Medicine, University of British Columbia, Vancouver, Canada

- Identified a novel serologic strain of toxoplasma gondii in German patients with ocular toxoplasmosis
- Seen in 44% of ocular toxo patients vs. 7% of non-ocular toxo patients
- Subjects with the ‘NR’ strain were ~3 times more likely to have recurrent disease than with other strains
- May be useful in predicting who is at risk for recurrence
Studied frequency of autoantibodies to ocular tissues in patients with JIA uveitis (47), idiopathic uveitis (12), JIA without uveitis (67), and healthy controls.

Overall 94% of JIAU had anti-uveal or retinal antibodies vs. 29% of controls.

Staining correlated with presence of complications.
TB or not TB, that is the question
Tested Quantiferon-Gold, TB-SPOT, and TST in 120 patients with uveitis in an endemic population

Found highest PPV and NPV for Quantiferon-Gold (0.372 PPV, 0.982 NPV)

Result held with sensitivity analysis
Frequency of positive tests is high in patients with suspicious features or history (~20-30%).

Protean clinical manifestations, but retinal vasculitis and serpiginoid uveitis are common.

Living in endemic area for more than 6 months is major risk factor for positivity.

False positive results from sarcoidosis in some studies.
Lack of Consensus in the Diagnosis and Treatment for Ocular Tuberculosis among Uveitis Specialists

Susan M. Lou, BA,1 Kelly L. Larkin, MD,2 Kevin Winthrop, MD, MPH,3 James T. Rosenbaum, MD,4,5 and members of Uveitis Specialists Study Group*

- Survey of 87 AUS members on likelihood of TB uveitis in two scenarios, lab tests requested, and treatment regimen
- No consensus on pre-test probability, laboratory testing
- No consensus on optimal duration of therapy in suspected cases
- No consensus on discontinuation in non-responders
Uveitis as a prognostic factor in multiple sclerosis

Erkingul Shugaiv, Erdem Tüzün, Murat Kürtüncü, Ash Kiyat-Atamer, Arzu Çoban, Gulsen Akman-Demir, Ilknur Tugal-Tutkun and Mefkure Eraksoy

Table 1. Comparison of clinical and demographic features of MS patients with and without uveitis.

<table>
<thead>
<tr>
<th>Feature</th>
<th>MS patients with uveitis (n = 41)</th>
<th>MS patients without uveitis (n = 100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (number of women)</td>
<td>35/41 (85%)</td>
<td>72/100 (72%)</td>
<td>0.12\textsuperscript{c}</td>
</tr>
<tr>
<td>Mean age at MS onset (SD, range)</td>
<td>31.1 (10.9, 13–52)</td>
<td>27.9 (9.1, 17–51)</td>
<td>0.09\textsuperscript{d}</td>
</tr>
<tr>
<td>Mean MS duration (years; SD, range)</td>
<td>10.6 (7.1, 2–30)</td>
<td>10.3 (8.2, 4–33)</td>
<td>0.26\textsuperscript{d}</td>
</tr>
<tr>
<td>Oligoclonal band positivity\textsuperscript{a}</td>
<td>33/41 (80%)</td>
<td>76/100 (76%)</td>
<td>0.66\textsuperscript{e}</td>
</tr>
<tr>
<td>RRMS</td>
<td>41/41 (100%)</td>
<td>64/100 (64%)</td>
<td>&lt;0.001\textsuperscript{c}</td>
</tr>
<tr>
<td>SPMS or PPMS</td>
<td>0/41 (0%)</td>
<td>36/100 (36%)</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>21/41 (51%)</td>
<td>36/100 (36%)</td>
<td>0.13\textsuperscript{c}</td>
</tr>
<tr>
<td>IFN or GA</td>
<td>27/41 (66%)</td>
<td>59/100 (59%)</td>
<td>0.57\textsuperscript{c}</td>
</tr>
<tr>
<td>NAT</td>
<td>3/41 (7%)</td>
<td>11/100 (11%)</td>
<td>0.76\textsuperscript{c}</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2/41 (5%)</td>
<td>12/100 (12%)</td>
<td>0.35\textsuperscript{c}</td>
</tr>
<tr>
<td>Median final EDSS score (IQR, range)</td>
<td>2.0 (1.7, 0.0–4.5)</td>
<td>3.0 (4.5, 1.0–9.5)</td>
<td>0.004\textsuperscript{e}</td>
</tr>
<tr>
<td>Median progression index (IQR, range)</td>
<td>0.2 (0.2, 0.0–1.8)</td>
<td>0.4 (0.4, 0.1–2.7)</td>
<td>&lt;0.001\textsuperscript{c}</td>
</tr>
</tbody>
</table>

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; SD: standard deviation; RRMS: relapsing–remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; IFN: interferon; GA: glatiramer acetate; NAT: natalizumab; IQR: interquartile range (difference between the upper and lower quartiles). \textsuperscript{a}Cerebrospinal fluid (CSF) oligoclonal bands (pattern 2 or 3), \textsuperscript{b}Progression index: EDSS/disease duration (years). \textsuperscript{c}Fisher’s exact test, \textsuperscript{d}Student’s t-test, \textsuperscript{e}Mann-Whitney U test.

- Study of 141 MS patients, 41 with uveitis
- All uveitic patients had relapsing-remitting form of uveitis
- Uveitis patients had less severe disease and less progression than non-uveitis patients
- Uveitis may be a favorable prognostic factor in MS
Characterisation of uveitis in association with multiple sclerosis

Wyatt Messenger, Lena Hildebrandt, Friederike Mackensen, Eric Suhler, Matthias Becker, James T Rosenbaum

- 196 eyes of 113 patients with MS and uveitis in retrospective review from two sites
- 80% intermediate uveitis, 15% anterior uveitis
- Median follow-up of 3 years
- 29% had MS diagnosed before uveitis; 15% simultaneous; and 56% had uveitis before MS diagnosis
- Prognosis no different from intermediate uveitis and generally good
Birds of a feather
Detection of choroid- and retina-antigen reactive CD8$^+$ and CD4$^+$ T lymphocytes in the vitreous fluid of patients with birdshot chorioretinopathy

Jonas J.W. Kuiper$^{a,b,*}$, Aniki Rothova$^{a,c}$, Peter A.W. Schellekens$^{a}$, Annette Ossewaarde-van Norel$^{a}$, Andries C. Bloem$^{d}$, Tuna Mutis$^b$

- Isolated T-cells from vitreous of 2 patients with BSCR
- CD4 and CD8 cells isolated, primarily Th1 CD4
- In one patient, T-cell receptor repertoire strongly skewed to oligoclonal receptors
- Cloned receptors react strongly with retinal and/or choroidal antigen
- Strongest evidence to date for autoimmune basis of BSCR, offers possibility of finding autoantigen

![Graph of IFN-γ levels](image-url)
Interleukin-17 production and T helper 17 cells in peripheral blood mononuclear cells in response to ocular lysate in patients with birdshot chorioretinopathy

Jonas J.W. Kuiper,1,2 Maarten E. Emmelot,2 Aniki Rothova,3 Tuna Mutis2

- Treated peripheral blood mononuclear cells of 19 BSCR pts with retinal and choroidal lysate
- Elevated IL-17 (but not IL-10 or IFN-g) production
- Higher numbers of Th17 cells after stimulation
- Suggests chronic Th17 activity in untreated BSCR
Correlation Between Clinical Signs and Optical Coherence Tomography With Enhanced Depth Imaging Findings in Patients With Birdshot Chorioretinopathy

Andrea D. Birnbaum, MD, PhD; Amani A. Fawzi, MD; Alfred Rademaker, PhD; Debra A. Goldstein, MD

- 14 BSCR patients studied with enhanced depth OCT
- Developed grading scheme including suprachoroidal fluid, RPE disruption, retinal thickening, and ellipsoid disruption
- High correlation between photopsias and suprachoroidal fluid; good correlation with vasculitis and vitreous haze
- Suggests ED-OCT may be useful in following disease activity and response to therapy
Examined outcomes of 92 eyes of 46 pts, followed an average of 57.2 months (with 17% > 10 years)

42 eyes treated ‘short term’ (< 1 year/episode), 50 treated ‘long term’

Both groups showed stabilization of improvement in mean deviation on fields, but PSD declined in short-term treatment group

Overall, treated patients maintain good central vision with BSCR, but visual fields are maintained better with long-term treatment
Outcomes

"I don’t like to speculate about outcomes, but be sure your account is settled by the end of the month."
Factors Predictive of Remission of New-Onset Anterior Uveitis

Pichaporn Artoonsombudh, MD,1,2 Maxwell Pistilli, MS,2 C. Stephen Foster, MD,1,3 Siddharth S. Pujari, MBBS, MS,1,4 Sapna S. Ganga, MD, MPH,5,6 Douglas A. Jabs, MD, MBA,7,8,9 Grace A. Levy-Cornea, MD,10 Robert B. Nussenblatt, MD, MPH,10 James T. Rosenbaum, MD,11,12 Eric B. Suhler, MD, MPH,11,13 Jennifer E. Thorne, MD, PhD,9,14 John H. Kempen, MD, PhD15,16

• Retrospective study through SITE of 687 patients with new onset anterior uveitis, for remission (90 days off medication) within 1 year
• Overall 47% of cases achieved remission
• Negative risk factors for remission include JIA, Behcet, bilateral disease, prior cataract surgery, low presenting acuity, vitreous cell, band keratopathy, and synechiae.

Figure 1. Kaplan-Meier estimation of the incidence of remission in cases with and without a systemic diagnosis of juvenile idiopathic arthritis.
• SITE study retrospective review of 1510 eyes with macular edema
• 52% improved 2 lines at 6 months
• Vision worse than 20/200, anterior uveitis, active uveitis at presentation all positive prognostic factors
• Snowbanking, posterior synechiae, hypotony negative risk factors
Outcomes of Changing Immunosuppressive Therapy after Treatment Failure in Patients with Noninfectious Uveitis

- Retrospective study of 147 pts with immunosuppression
- 55% eventually required change of regimen or addition of new agent
- Visual acuity falls with successive changes
- 80% of patients switched to biologics achieved treatment ‘success’; higher proportion than switching to other IMT
SITE study of periocular injections

Followed 1192 eyes of 914 patients.

72% achieved control of uveitis by 6 months

At 12 months, 34% with IOP>24 and 15% with IOP>30

At 12 months, 14% requiring cataract surgery
Drugs, drugs, and more drugs

"The problem is that you're overmedicated. Luckily there are drugs that can help with that."
95 patients from Campinas, Brazil with active recurrent ocular toxoplasmosis.

All treated initially with Bactrim bid x 45 days

Randomized to QOD Bactrim or placebo and followed for 1 year

0/46 recurrent in treatment group vs. 6/47 in placebo group

No toxicity or side effects noted in treatment group
Prospective study of 80 patients with non-infectious uveitis requiring IMT randomized to 25 mg weekly MTX vs. 1 g bid MMF; endpoint quiet disease with prednisone ≤ 10 mg.

No significant difference in outcomes, although 69% achieved success with MTX vs. 47% with MMF.
• Retrospective study of 82 eyes receiving 142 injections
• ~40% with 3 line improvement at 1 month, ~60% at 12 months
• 30% IOP elevation of > 10 mm at 1 year with 25% having IOP > 25 mm
• Mean time to reinjection ~6 months
• 10% rate of cataract surgery at 1 year in phakic pts
• Retrospective study of 54 injections (400 ug MTX) in 38 eyes of 30 patients with chronic uveitis
• 30 eyes responded to treatment
• Of these, 73% entered long lasting (> 1 year) remission following single injection
• Overall median time to relapse 17 months
• Most eyes responded to repeat injection
Biologics
Prospective double-masked Phase I/II trial
12 patients with refractory scleritis (failed prednisone + 1 IMT)
9/12 met endpoint
7/9 required reinfusion at 6 months
Treatment well-tolerated
Long-Term Effects of Tocilizumab Therapy for Refractory Uveitis-Related Macular Edema

Marina Mesquida, MD, Blanca Molins, PhD, Victor Llorens, MD, PhD, Maite Sanz de la Maza, MD, PhD, Alfredo Adán, MD, PhD

- 11 eyes of 7 patients with chronic macular edema (mean 14 years!) recalcitrant to treatment with corticosteroid and IMT/biologics
- Tocilizumab given at 8 mg/kg every 4 weeks
- All patients achieved uveitis remission with prednisone < 10 mg daily +/- MTX
- Central thickness decreased from 550 μM to 274 μM at 1 year
- 2 patients discontinued (remission) recurred within 3 months

Figure 1. Graph showing the evolution of mean central foveal thickness (CFT) in study eyes (n = 11). Statistical analysis was conducted using the Wilcoxon test (*P < 0.05).

Figure 2. Graph showing mean changes in best-corrected visual acuity (BCVA) in the study eyes (n = 11). Statistical analysis was conducted using the Wilcoxon test (*P < 0.05). logMAR = logarithm of the minimum angle of resolution.
Evaluation of the Long-Term Efficacy and Safety of Infliximab Treatment for Uveitis in Behçet’s Disease

A Multicenter Study

- 164 patients with Behcet treated with infliximab for > 1 year
- Frequency of attacks decreased from 5.3/year to 1.4/year
- Visual acuity improved in all groups
- 15% discontinued due to adverse events (infusion reaction) or insufficient efficacy
• Extensive review of literature with quality assessment
• Strong recommendations
  – Infliximab and adalimumab be considered first line treatments in Behcet disease
  – These agents be considered second line agents in JIA
  – These agents be considered in other forms of uveitis recalitrant to IMT
  – Infliximab and adalimumab be considered in preference to etanercept for uveitis
• Hope that this review is useful in obtaining coverage for patients potentially benefiting from these drugs
Quality and cost
Psychometric evaluation of the National Eye Institute Visual Function Questionnaire and Visual Function Questionnaire Utility Index in patients with non-infectious intermediate and posterior uveitis

Rupali K. Naik · Katharine S. Gries · Anne M. Rentz · Jonathan W. Kowalski · Dennis A. Revicki

- Quality of life surveys done in the Ozurdex uveitis trials
- Assessed with VQF-25, VQF-UI, SF-36, SF-6D, EQ-5D
- VQF-25 and VQF-UI were internally consistent and reliable
- Correlation with SF-6D and EQ-5D were small to moderate
- VQF-25 and UI correlated with improvements in visual acuity

- 80 subjects with non-infectious uveitis tested with VQF-25 and SF-12, divided between medical and local treatment
- Median VQF-25 score of 78.6
- Visual acuity of better and worse eye correlated with VQF
- Medical comorbidity associated with SF-12 measure
- No difference in change in scores with type of therapy -> systemic therapy does not decrease QOL relative to local therapy

Original Article

Quality of Life in Patients with Noninfectious Uveitis Treated with or without Systemic Anti-inflammatory Therapy

Wei Gui, BS1, Matthew Dombrow, MD2, Inna Marcus, MD3, Meredith H. Stowe, PhD2, Baylah Tessier-Sherman, MPH2, Elizabeth Yang, MD4, and John J. Huang, MD1
Calculated total cost for each arm of the MUST trial as well as $/QALY.

Total cost in bilateral group was $69,300 for implant and $52,500 for systemics.

For unilateral disease, costs were not significantly different.

Minimal QALY changes in either group (as measured by EQ-5D).

Sensitivity analysis suggested implants unlikely to be cost effective (<$100K/QALY) for bilateral disease, possibly for unilateral disease.
Healthcare costs and utilization for privately insured patients treated for non-infectious uveitis in the USA

David S Chu¹,², Scott J Johnson³, Usha G Mallya⁴, Matthew R Davis⁵, Rachael A Sorg⁴ and Mei Sheng Duh³

- Analyzed database of 80M insured individuals with diagnoses of uveitis
- Compared payer costs per month for patients on corticosteroids, immunosuppressants, and biologics
- Monthly costs $935 for corticosteroids, $1738 for IMT, and $1439 for biologics
- Extrapolating, burden/month of uveitis treatment is $16M/month or $195M/year
Case of the year

Case Report

Bilateral Acute Anterior Uveitis and Optic Disc Edema Following a Snake Bite

Praveen K Kumar, Shashi Ahuja, Praveen S Kumar

Department of Ophthalmology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Fig. 1. (A) Slit-lamp photograph of the right eye showing posterior synchiae at the 3 o'clock position. (B) Slit-lamp photograph of the left eye showing posterior synchiae at the 11 o'clock position.

Fig. 2. Fundus photographs of the left (A) and right eye (B) showing hyperemia and blurred margins, with edema of the optic nerve head.
Thank you!