Uveitis literature review 2017

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Disclosures

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

• RVG laboratory received research funding in 2017 from:
  – National Eye Institute
  – Research to Prevent Blindness
  – NovaBay Pharma
  – Omeros Pharma

• Received no direct compensation
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 (10/1/16 to 9/30/17)
- Selected ~ 20 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 2016-17

- 1664 papers in English
- 648 human
- 214 reviews
- 35 clinical trials
Most cited uveitis papers from 2015

Persistence of Ebola Virus in Ocular Fluid during Convalescence

Jay B. Varkey, M.D., Jessica G. Shantha, M.D., Ian Crozier, M.D.,
Colleen S. Kraft, M.D., G. Marshall Lyon, M.D., Aneesh K. Mehta, M.D.,
Gokul Kumar, M.D., Justine R. Smith, M.B., B.S., Ph.D.,
Markus H. Kainulainen, Ph.D., Shannon Whitmer, Ph.D., Ute Ströher, Ph.D.,
Timothy M. Uyeki, M.D., M.P.H., M.P.P., Bruce S. Ribner, M.D., M.P.H.,
and Steven Yeh, M.D.

139 citations

Microbiota-Dependent Activation of an Autoreactive
T Cell Receptor Provokes Autoimmunity
in an Immunologically Privileged Site

Roiko Horai,1,4 Carlos R. Zarate-Bladés,1,4 Patricia Dillenburg-Pilla,2 Jun Chen,1,4 Jennifer L. Kielczewski,3
Phyllis B. Silver,1 Yingying Ji,1,2,4 Chien-Chung Chan,1 Hidehiro Yamane,1 Kenya Honda,1,5 and Rachel R. Caspi,1,4

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6RIKEN Center for Integrative Medical Sciences, Yokohama 224-0022, Japan

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Catarina, Florianópolis, SC 88040-900, Brazil
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54 citations
...but first, a shameless self-plug for my lab members
Intraperitoneal injection of the compound Luminol allows bioluminescent, longitudinal monitoring of primed mycobacterial uveitis.
Using a combination of qPCR and BRiSK, the authors find relative few bacteria on healthy conjunctiva (1/50 cells).

Unexpectedly find the virus torque teno virus in nearly 50% of healthy conjunctiva.
Basic training
Zika infection known for past 2 years to cause variety of uveitis presentations

- Injected mice systemically with Zika virus
- High expression in cornea, tears, lacrimal glands, retina, and optic nerve
- Clear uveitis phenotype
Metabolites of bacterial fermentation of dietary fiber

When fed orally to C57BL/6 mice, propionate and butyrate attenuated EAU

Appeared to accentuate Treg activation

Reduced trafficking of immune effector cells from gut to spleen
Dense genotyping of immune-related loci implicates host responses to microbial exposure in Behçet’s disease susceptibility

- 1900 Turkish Behcet cases and 1779 controls genotyped with Immunochip
- HLA-B51 major risk
- IL1-A/B, IRF8, CEBPB-PTPN1 all significantly associated
- Replicated in Iranian and Japanese populations
- Shared with Crohn’s disease and leprosy
- Implicates innate immune response to microbes
In Translation
Increased Serum Antibody Titer against HPV-16 Antigen in Patients with Behçet’s Disease

Kyu Yeun Kim,1* Do Young Kim,2* Jimyung Seo,2 Yuri Ahn,2 and Dong Soo Kim1

Quadrivalent human papillomavirus (HPV) vaccine has been reported to be significantly associated with Behçet’s disease (BD). However, no reports have described HPV infection as a possible cause for the development of BD. The objective of this study was to evaluate whether anti-HPV immunoglobulin G (IgG) antibody titer is increased in BD. Serum samples from 93 Korean BD patients, who fulfilled the diagnostic criteria of the International Study Group for BD, were used in an enzyme-linked immunosorbent assay (ELISA). The clinical activity of BD was evaluated at the time of blood sampling. HPV-16 L1

- Quadrivalent HPV vaccine has been associated with Behcet
- 93 BD patients and 40 controls tested for antibody to HPV16
- Significantly higher titers in BD patients; for those with OD > 2 on ELISA 100% specificity and sensitivity
• 34 macaque monkeys injected either subretinal or intravitreal with AAV-8 vector, low or high dose
• 28 or 90 day protocol
• Both innate and adaptive systems significantly activated
• Persistent AC and vitreous cell in some animals
Studied 10 epiretinal membranes in patients with sarcoidosis by immunohistochemistry

4/10 showed granulomas

5/10 stained positive for *P. acnes*

0/10 stained positive among control ERM
Grotting et al.: 100 patients/100 controls
- Vit D levels 31.2 ng/mL in controls, 26.3 ng/mL in uveitis patients
- Suggests 4% lower odds of developing uveitis per 1 ng/mL increase in vit D

Dadaci et al.: 20 AAU patients and 20 controls
- All with 3+ to 4+ AC cell and off systemic medications at time of sampling
- 2 fold higher vitamin D in control group
• Measured cytokine levels in 10 patients AC tap and serum with ARN, 18 with Fuchs/Rubella, 20 with ocular toxoplasmosis; 7 controls
• Unique profile associated with each infectious agent
New integrated 30 g short needle and pipette bulb

Tested on 301 aqueous samples over 6 years

No complications reported

Joins ranks of O’Rouke and ‘minim’ devices; confirms safety of AC paracentesis
Objective Quantification of Anterior Chamber Inflammation

Measuring Cells and Flare by Anterior Segment Optical Coherence Tomography

- Performed SS-OCT of anterior segment in 70 eyes with active uveitis, 97 with inactive uveitis, 70 controls
- Counted cells manually in tomographic sections
- Calculated aqueous-air-relative intensity (ARI)
- Strong correlation of OCT indices to traditional cell and flare
Cohort study of 435 children diagnosed with JIA between 1997 and 2000

- 89 (21%) developed uveitis over course of study
- Confirmed age < 7 and ANA as predictor
- Showed antihistone antibodies (AHA) stronger predictor than either for development of uveitis
This year’s new model
Vogt-Koyanagi-Harada disease-like posterior uveitis in the course of nivolumab (anti-PD-1 antibody), interposed by vemurafenib (BRAF inhibitor), for metastatic cutaneous malignant melanoma

Toshihiko Matsuo & Osamu Yamasaki

Case Report
Uveitis induced by programmed cell death protein 1 inhibitor therapy with nivolumab in metastatic melanoma patient
Hiroaki Kanno, Kyoko Ishida, Wataru Yamada, Takashi Nishida, Nobumichi Takahashi, Kiyofumi Mochizuki, Tomoko Takahashi, Mariko Seishima

LETTER TO THE EDITOR
Uveitis and Papillitis in the Setting of Dabrafenib and Trametinib Therapy for Metastatic Melanoma: A Case Report
Jennifer Lim, Anna J. Lomax, Catriona McNeil, and Brian Harrisberg

Ocular toxicity due to Trametinib and Dabrafenib
Stephanie Sarny, Michael Neumayer, Julian Koffer, and Yosuf El-Shabrawi
Biologic-al
Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis

Athimalaipet V. Ramanan, F.R.C.P.C.H., F.R.C.P.,
Andrew D. Dick, M.B., B.S., M.D., Ashley P. Jones, Ph.D., Andrew McKay, M.Sc.,
Paula R. Williamson, Ph.D., Sandrine Comperot-Lacassagne, M.D.,
Ben Hardwick, M.Res., Helen Hickey, B.Sc., Dyfrig Hughes, Ph.D.,
and Michael W. Beresford, M.B., Ch.B., Ph.D., for the SYCAMORE Study Group.

- Multicenter double-masked RCT of 90 subjects for adalimumab + MTX vs. MTX alone for JIA-associated uveitis
- 27% fail rate treated at 2 years vs. 60% MTX only
- AE 10 events/year vs. 6.5/year with MTX only; 0.29 SAE/yr vs 0.19 SAE/yr
Adalimumab for Treatment of Noninfectious Uveitis

Immunogenicity and Clinical Relevance of Measuring Serum Drug Levels and Antidrug Antibodies

- 25 patients treated with adalimumab for uveitis
- 72% with favorable response
- Trough levels of adalimumab correlate with response
- 4 patients with persistent anti-adalimumab antibodies had undetectable drug levels
- No protective effect of concomitant IMT (1 each CsA, MMF, MTX)
- Suggests a subset of adalimumab treatment failures due to AAA
54 consecutive patients treated with adalimumab for Behçet disease followed over 48 months
• 90% response to therapy
• At 48 months, 17 discontinued (4 due to adverse effects, 5 for primary inefficiency, 7 for late insufficiency, 1 for pregnancy)
• Presence or absence of DMARD treatment did not affect retention
25 patients with JIA-associated uveitis who had failed MTX and biologics (mostly anti-TNF)

- 8 mg/kg tocilizumab monthly

- ~80% with improvement in AC cell

- Significant improvements in central macular thickness and visual acuity

- Two patients discontinued due to autoimmune thrombocytopenia
37 patients enrolled in two dose RCT for tocilizumab for non-infectious intermediate, posterior, and panuveitis

- At 6 months, substantial improvement in visual acuity and central retinal thickness in both groups
- Lower dose group showed better effect than higher dose group
- Well tolerated with few SAE
• 16 eyes of 12 patients with refractory CME
  – 2/3 with JIA or BSCR
  – 10 post-Ozurdex
• Treated with tocilizumab 8 mg/kg q 4 weeks
• 14/16 with significant improvement at month 12
• BCVa improved in 14/16, stable in 2/2
• 5 patients discontinued at month 12 all had recurrent CME
Drugs, drugs, drugs
• RCT comparing enteric coated mycophenolate sodium vs. placebo in chronic intermediate uveitis

• 41 patients randomized to prednisolone +/- MPS

• Strict criteria for relapse

• 15 month year survival ~52% in treatment vs. 19% placebo
- Brimapitide (XG-102) is a local JNK inhibitor
- Single subconjunctival injection of 90 or 900 ug post-complicated intraocular surgery (retina, glaucoma, combined)
- Equivalent AC grades to dexamethasone drops qid
- 15-20% of patients required some local steroid rescue
- No difference in AE or SAE
- Potential utility for uveitis to be explored
• 7 year follow-up from MUST
• ~70% of patients initially randomized, 328 eyes total
• Visual acuity at 7 years favored implant by 7.2 letters
• Complications comparable except hyperlipidemia, hypertension, fractures, and antibiotic-related infections
• Hospitalizations slightly higher in the implant group
• NEI VFQ-25 visual function questionnaire given the MUST participants for 3 years
• At 3 year point, both groups improved ~10 points and equivalent
• Improvement more immediate for implant group
Corticosteroid-Related Adverse Events Systematically Increase with Corticosteroid Dose in Noninfectious Intermediate, Posterior, or Panuveitis

Post Hoc Analyses from the VISUAL-1 and VISUAL-2 Trials

- Measured frequency of steroid-related AE in VISUAL-1 and -2
- Rates high in both studies during steroid use phase (454 and 317/PY vs 36 and 41/PY off steroids)
- Each 10 mg increase in dose was associated with 1.5 to 2.6-fold increase in steroid-related complications
Risk of Ocular Hypertension in Adults with Noninfectious Uveitis

- Retrospective study of 5270 eyes of 3308 patients
- Annual incidence of iop > 21 = 14%, > 30 = 5%
- Among positive predictors: PPV, systemic HTN, contralateral OHT, corticosteroid use
Antibodies anybody?
• Studied 25 patients with AZOOR
• Characterized fundus and autofluorescence findings
• Ran 1D Western antiretinal antibodies – all patients positive, average of 6.6 bands/patient (vs ~1/control)
Antigen bead array with 188 antigens from 97 ocular proteins used on 24 patients with AIR, 151 with uveitis, 21 with cataract

- Anti-recoverin found in 12% of AIR, 5% of cataract, 1.3% of uveitis
- No association of malignancy and anti-recoverin
- 1 or more bands found in 63% of AIR, 55% of uveitis, 48% of cataract
- Antibodies against photoreceptor-specific nuclear receptor and RBP3 were more common in AIR than uveitis
• Measured serum binding to specific retinal proteins in 18 uveitis and 6 control patients by surface plasmon resonance

• Anti-recoverin reactivity found in 14/18 uveitis and 0/6 control subjects

• 11/11 BSCR patients with positive reactivity
A picture is worth...
Analyzed choroidal thickness and choroidal reflectivity in 386 eyes with BSCR vs 59 controls
- Higher choroidal reflectivity and lower choroidal thickness seen in inactive BSCR than active disease or controls
- Strong negative correlation between reflectivity and choroidal thickness
- May be useful marker for disease progression
• 132/172 (79%) eyes showed abnormalities of FAF
• Most common were peripapillary hypofluorescence, granular macular and peripheral hypofluorescence
• Confluent hypofluorescence correlated with worse visual acuity
Pot pourri
• Gave personality tests to 93 patients with uveitis and 93 gender- and age-matched controls
• 25 question
• Uveitis patients scored higher on social, calm, organized, accommodative, and inquisitive scales
• Control patients scored higher on reserved, limbic, unstructured, and non-curious
• Calm personality associated with HLA-B27 specifically
Letter to the Editor

‘Bung’ eye: ocular inflammation caused by sandfly bite

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and Geoffrey C Lam FRANZCO
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Received 27 February 2017; accepted 2 May 2017.

Figure 1. (a) Case 1 – hypopyon in right eye with presumed bite mark at 4 o’clock. (b) Case 2 – haemorrhagic hypopyon in left eye with trickling WBCs at presumed site of bite.
Conclusions: As exotic pets become more and more popular, the importance of wearing ocular protection when handling tarantulas should be emphasized when they are sold. Tarantulas are unsuitable pet for children. When a patient presents with an unusual red eye, pet-keeping history, spiders included, should be asked.
Thank you!