

Minutes/Summary

Autoimmune Retinopathy (AIR) Workshop: from Diagnosis to Treatment 9/27/13

Attendees:

H. Nida Sen, Chi-Chao Chan, Wendy Smith, Ping Chen, Debra Goldstein, Phil McCoy, Elena Stansky, Pradeep K Dagur, Lai Wei, Nicholas Butler, Robert Nussenblatt, Paul Sieving, Grazyna Adamus, Lynn Gordon, Bryce Binstadt, Richard Lee, Careen Lowder, John Heckenlively, Catherine Morgans, Wadih M. Zein, Lisa Faia, Janet Davis, Cathy Cukras, Brett Jeffrey, Nirali Bhatt, Susan Hannes, Zhiyu Li, Paul Yang, Dhanu Meleth, David Valent, Baoying Liu, John Hooks, Barbara Detrick, Monica Dalal, Will Tucker, Mary Beth Aronow, William Paul, Patti Sherry, Austin Fox

Program

Paul Sieving, MD, PhD; Director of the National Eye Institute: Dr. Sieving opens the workshop and welcomes all attendees. Dr. Sieving goes on to discuss melanoma associated retinopathy (MAR) and how anti-retinal antibodies (ARAs) were discovered and used to modulate retinal circuits, pathways, and vision in humans.

H. Nida Sen, MD, MHSc; NEI: Historical benchmarks of AIR are discussed, highlighting the first reports and characterization of paraneoplastic retinopathies (CAR & MAR) and nonparaneoplastic autoimmune retinopathy (npAIR) as well as treatment benchmarks.

The goal of the AIR workshop is to further develop consensus for diagnosis and treatment of npAIR.

Grazyna Adamus, PhD; Casey Eye Institute, OHSU: Molecular mechanisms of retinal damage are discussed. The role of autoantibodies in CAR, MAR, as well as other ocular diseases are highlighted. The pathogenicity and mechanism of retinal degeneration related to recoverin, alpha-enolase, and carbonic anhydrase II are discussed.

Catherine Morgans, PhD; Casey Eye Institute, OHSU: Studies on autoantibodies specific to MAR patients are characterized, specifically relating to TRPM1&3 channels, focusing on their pathogenicity and how this contributes to an altered ERG in MAR.

John Heckenlively, MD; Kellogg Eye Center, UM: The approaches and challenges to recognize retinitis pigmentosa patients with AIR is discussed. The clinical characterization of AIR patients and features to help distinguish between AIR, RP with secondary AIR are discussed. The need for studies to examine cellular immunity and to identify diagnostic/therapeutic response biomarkers in AIR is stressed.

Robert Nussenblatt, MD, MPH; NEI: Autoimmunity in eye disease is examined. Studies relating to autoimmune animal models and the prevalence and significance of ARAs in normal controls and patients with uveitis, AMD, and chronic toxoplasma gondii infection. The concept of anti-idiotypic antibodies in autoimmunity is explained as it is one possible explanation to autoimmune diseases and AIR. Other possible explanations for autoantibodies in AIR are encouraged.

Lynn Gordon, MD; Jules Stein Eye Institute: The presence of ARAs in healthy individuals and other systemic autoimmune diseases is explored. In the absence of retinopathy, anti-recoverin antibodies has been seen with lung cancer and alpha-enolase antibodies has been seen with lung cancer, autoimmune hepatitis, rheumatoid arthritis, mixed cryoglobulinemia, multiple sclerosis, & normal controls. The basics of antibody testing is surveyed. The issue of variability in ARA testing among labs is discussed. A study examining the presence of ARAs against retinal antigens in normal controls and patients with glaucoma, sarcoidosis, lung disease, multiple sclerosis is examined.

Bryce A. Binstadt, MD, PhD; University of Minnesota: A focus on B cells and the possible benefits of B-cell targeting therapies is discussed. The FDA-approved B cell therapies rituximab (anti-CD20) and belimumab (anti-BLyS) are discussed. Rituximab is FDA-approval for NHL, CLL, RA if anti-TNFs ineffective, ANCA vasculitis (Wegener's & MPA). Belimumab is FDA-approval for SLE in presence of ANA or anti-dsDNA antibodies. Mechanisms, indications, and off-label use of B cell therapy is examined along with related studies. Multiple issues of understanding autoimmune disease and AIR are discussed regarding autoantibody pathogenicity, B cell pathogenicity, therapy, and prognosis.

Wendy Smith, MD; Mayo Clinic: Topics relating to the treatment of AIR are examined including treatment challenges and the lack of clear guidelines for managing immunosuppressives in the treatment of AIR. The most current AIR treatments are surveyed including corticosteroids, conventional immunosuppressives, biologics, IVIG, and plasmapheresis. Several studies and case reports/series on treatments of AIR are highlighted. The issue of quantifying treatment response and prognostic indicators in AIR is examined. Highlighted points include: better understanding of ARAs & retinal dysfunction is needed to improve treatment, paraneoplastic AIR responds better to treatment than npAIR, and imitations in diagnostic assays limit therapeutic investigations.

H. Nida Sen, MD, MHSc; NEI: The results of a survey of American Uveitis Society members regarding diagnosis and treatment of AIR are reported. In this process, discussion on developing a consensus for the diagnosis and treatment of AIR is mediated by Dr. Nida Sen. (*See consensus discussion notes below.*)

Janet Davis, MD; Bascom Palmer Eye Institute: The possible role of retinal biopsy to diagnose AIR is examined. Other diseases in which biopsy are used include lymphoma and chorioretinitis. The anatomical location where the biopsy would be performed, how a specimen should be handled, tests that could be performed on a biopsy specimen, and how biopsy and testing would improve patient care are discussed.

Debra Goldstein, MD; Northwestern University: Several cases were presented to highlight examples and make several points one should consider when diagnosing AIR: Diagnosis of AIR is a clinical diagnosis- History, exam, especially OCT are crucial; Blood tests don't make the AIR diagnosis- Not all patients with ARAs have AIR; ARA testing should not be routine in the work-up of decreased vision.

Brett Jeffery, PhD; NEI: An overview of the NEI experience with ERG's in AIR patients is discussed. The basics of ERGs are briefly discussed. Several ERGs are shown to make the following points: earliest changes in AIR patients seen are reduction in cone ERG amplitude on ff/mfERG, rod loss occurs in advanced AIR stages, and unilateral ERG reductions were seen in only 4/25 pts.

Wadiah Zein, MD; NEI: The complexity of AIR is stressed, and overlapping features as well as more specific features of npAIR and hereditary retinal degenerations (cone dystrophy, CRD, CD) are highlighted through case presentations.

Grazyna Adamus, PhD; Casey Eye Institute, OHSU: The basic concepts of Immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA), and Western Blotting (WB) are described. WB and IHC for detecting ARAs for paraneoplastic AIR is detailed and described as this occurs in the Ocular Immunology Laboratory at OHSU. IHC: highlights which cellular structures are labeled by autoantibodies in the retina. WB: recommended for further evaluation of ARA specificity; more sensitive, shows binding to linear epitopes in antigenic proteins. The importance of using human tissue to test for ARAs for diagnostic purposes is highlighted; however, the availability of human tissue is limited. Need for standard laboratory protocol to detect ARAs is addressed: laboratories need to be CLIA-certified to conduct AIR/ARA diagnostic testing.

Chi-Chao Chan, MD; NEI: The concept of IHC and ELISA and its use in the detection of ARAs is detailed. IHC images are shown in examples of IHC use to detect ARAs using human & monkey retina as specimens.

John Hooks, PhD; Former Chief of LI, NEI and Barbara Detrick, PhD; John Hopkins University SOM: Evaluation of ARAs in historical studies is discussed. Epitopes of antigens in ECOR (Alpha fodrin and Villin-2) and ARAs (ATR-X and LEDGF) are identified and discussed. The detection of ARAs in AIR samples at the NEI using indirect IFA, confocal microscopy, and pathology examination is reviewed and detailed.

Testing strategies to detect ARAs is evaluated. Examples of the testing strategy used for autoimmune disease (SLE) and infectious disease (lyme, hep C, syphilis) are given. It was proposed to use 2-step assay system to identify ARA reactivity and identifying a specific epitope for confirmatory/secondary testing systems: screening assays would include IFA and WB; secondary tests might include EIA, WB, and Slot blot.

Characteristics of ARA IFAs are discussed. Precautions are discussed including identifying a normal range with dilutions to reach high level of specificity and cross reactivity of other antibodies/antigens. Future directions of laboratory approaches to evaluating AIR are discussed.

It was stressed that it is imperative that we identify a testing and standardized assay for detecting ARAs and diagnosing AIR in order to develop diagnostic criteria for AIR, which would allow better treatment of AIR.

Phil McCoy, PhD; NHLBI: The trans-NIH Center for Human Immunology and capabilities of immunophenotyping B cells, specifically Comprehensive Leukocyte ImmunoPhenotyping (CLIP), were discussed. Results of immunophenotyping of AIR and uveitis patients and how these compare with healthy normal controls are reported: in AIR, there is a probable increase in naïve B cells and decrease in switched

memory B cells (IgD-CD27+), plasmablasts do not appear increased, and there is a possible shift in isotype expression in B cells of AIR patients; however, more power is needed to draw meaningful conclusion.

Lai Wei, M.D., PhD; NEI: The potential for epigenetic studies in AIR are discussed. The concept of epigenetics is introduced. The use of next generation sequencing (NGS) is detailed and explained as a possible future applications for understanding and impacting the diagnosis and management of AIR patients.

H. Nida Sen, MD, MHSc; NEI: A pilot clinical trial in which the efficacy and safety of rituximab was studied for treatment of AIR is discussed. A case of an AIR patient who improved clinically after Rituximab therapy is presented. Results of this clinical trial are detailed. The need for randomized trials is stressed as this pilot clinical trial of a small cohort showed that rituximab was well tolerated and may have a role in the treatment of AIR.

All attendees are thanked for attending AIR workshop as progress toward the goal of developing a consensus for the diagnosis and treatment of npAIR was made. Attendees are notified that a survey would be sent out to follow up and establish a final consensus.

Consensus discussions notes: Developing a consensus for the diagnosis and treatment of npAIR
(Mediated by Dr. H. Nida Sen and panel discussions.)

Essential Criteria

1. Antiretinal antibodies are essential component to diagnosis of AIR
 - “Antiretinal antibodies are not sufficient to make diagnosis of AIR” but they have to be present or the diagnosis is not correct.
 - Must accept strengths and weaknesses of tests-like false negatives
 - Need to differentiate ARAs, such as anti-recoverin from the rest
 - 100% necessary
2. Absence of another reason for ARA development such as RP, birdshot, AZOOR, or overt inflammatory disease is necessary
 - “Overt inflammatory disease”: best way to phrase is “inflammatory change is not sufficient to explain vision loss”
 - In defining overt inflammatory disease- best to be strict and consistent with the diagnosis-(Once we get a handle on that, then we can begin to expand)
 - Since we are trying to define primary npAIR, then we need to exclude inflammatory ones. This doesn’t mean you can’t get secondary npAIR in uveitis.
 - Let’s say we see no more than 3 cells
 - Should be essential criteria
 - How would we include antibodies that have gone away with treatment? It would be hard for criteria to address patients who were treated first without checking ARAs.
 - 2 reasons to create diagnostic criteria: 1. Make diagnosis clinically to act/treat as a treating physician. 2. Make diagnosis for research purposes(Rheum has done this well multiple times)
 - Criteria differ based on their purpose; therefore, we need to be clear if this is for clinical and research purposes.
 - We need to define phenotype before addressing biomarkers.
3. Absence of fundus lesions or degeneration that can explain the visual field or ERG loss (just like multifocal choroiditis). Should say “retinochoroidal lesions”?
 - “Overt retinal dystrophy or RP” because you can get pigment deposits in advanced stages of an end-stage disease, which is hard to define, so we are assuming more fresh cases.
 - Vascular narrowing and pigmentary changes, depends on stage of disease.
 - These include fundus lesions-explaining visual field and ERG loss.
 - Consider these supportive.

4. ERG abnormality +/- visual field changes-using full-field ERG rather than multifocal ERG

Supportive Criteria

- Should we include nyctalopia, photoaversion, dyschromatopsia as supportive?

- It is more the recent onset that suggests AIR
- It depends on where in disease the patient makes entry the diagnosis.
- Because you see these symptoms in other diseases, they are included in the supportive criteria and not essential.
- We should maybe put this historical information & rapidity of onset into essential criteria.
- What is recent? What if these changes started 5yrs ago?
- OCT: Are we going to put OCT in here? Problem is that the disease must be central for OCT to be useful, so it could be supportive.
- FA: Should we see leakage on FA? Only seen in a small majority of uveitis patients, but could this be supportive? Optos?
- AF: Should autofluorescence be used to exclude patients?
 - Central foveal hypofluorescence-cone dystrophy vs clear parafoveal ring of hypofluorescence-(retinal atrophy?)
- Autoimmune history: Should we include autoimmune history? How would you define and what would be included in autoimmune history? Family history?
- AGE: Is age an important criteria?
- Building consensus using cases
 - exactly what is being done right now with SUN
 - Questions of how SUN and submitting cases works.
 - Could Jabs use SUN site and present to a smaller panel?-costly to do this and he may not support
 - We should consider doing this from NEI
- Essential criteria has 2 No's and 2 things that you run the test but nothing to say why you did them in the first place. So what if somebody gets antiserum antibody testing and gets a positive result?:
 - Think of it like Behcet's IUSG criteria. The clinical judgment still has to play a role. You don't send B51 on every uveitis patient initially. You look @ FA, look at the patient, and take a history and then you send out a B51.
 - We hope that ARAs will be like that too and that's a challenge in defining the clinical criteria.
 - That's why I would like to put the actual clinical criteria up there, so if that basic clinical criteria, when a new patient is worked up and no recent onset of photopsias and a decrease in vision that is recent, then you shouldn't need to be considering it and stop ordering the tests.
 - Essential criteria means that they need to have all of it, not just one.
 - What I want is to stop ordering the tests when the diagnosis is not possible. So I would put the history as essential criteria, because all of my patients had nyctalopia, photoaversion, dyschromatopsia and none had npAIR.

Establishing Final Consensus

To fully develop an expert consensus for diagnostic criteria for non-paraneoplastic Autoimmune Retinopathy (npAIR), a survey was developed after conducting the AIR Workshop on 9/27/13. The survey addresses the clinical and basic science aspects of the npAIR diagnosis and incorporates the expert opinions given at the AIR Workshop (summarized above). To develop consensus, the survey utilizes the Delphi process, a consensus-building method in which experts are encouraged to revise their previous answers in light of the replies of other members of their panel. The survey is currently being conducted through the Clinical Trials Database at NIH. When consensus is established on diagnostic and treatment, a manuscript will be prepared to publish these diagnostic and treatment criteria for the management AIR.

AIR WORKSHOP PROGRAM:

Title: **Autoimmune retinopathy (AIR) workshop: from diagnosis to treatment**

September 27, 2013 8:00AM to 3:30PM

Cogan Library, Building 10, 10th floor, room: 10N202

1. **8:00 AM-8:15 AM Introduction/Welcome (Dr Sieving)**
2. **8:15-8:30 Historical benchmarks in autoimmune retinopathies (Sen)**
3. **8:30-9:30 Paraneoplastic Retinopathies and mechanisms:**
 - a. Antiretinal antibodies: mechanism of injury (Adamus) (20)
 - b. MAR, TRPM1 and what we can learn from it (Morgans) (20)

Discussion (15)
4. **9:30-10:30: Autoimmune retinopathy as a complication of retinal disorders:**
 - a. Autoimmune retinopathy as an exacerbation factor in retinitis pigmentosa (Heckenlively) (15)
 - b. Autoantibodies in AMD and uveitis (Nussenblatt) (15)
 - c. Antiretinal antibodies in healthy individuals and other systemic autoimmune diseases (i.e., MS) (Gordon) (15)

Discussion (15)
5. **10:30 -11:00: Defined autoantibody mediated rheumatologic disorders-What can we learn?** (Binstadt) (30 minutes)
6. **11:00-11:20: Current treatments in AIR (both paraneoplastic and nonparaneoplastic) (Smith) (20 mins)**
7. **11:20-12:35 pm: What is Nonparaneoplastic Autoimmune retinopathy?**
 - a. Developing consensus on the phenotype of the disease: results of a survey among AUS members (Sen) (15 minutes)
 - b. What's the best way to diagnose AIR, should retinal biopsy be considered? (Davis)(15 minutes)
 - c. How difficult is the diagnosis: Case examples (Goldstein) (10mins)
 - d. Electrophysiologic testing in AIR: Brett Jeffrey (15 minutes)
 - e. Overlapping features of npAIR with genetic retinal disorders (Zein) (15 minutes)
 - f. **Panel discussion: Goldstein, Nussenblatt, Heckenlively, W Smith (15)**
 - i. **Consensus voting on clinical criteria for npAIR (~15 mins)**

Lunch Break: 12:35-1:20pm

8. **1:20-2:30pm: Antiretinal antibody testing-Ups and Downs in the last decade**
 - a. **Panel to pose questions: Bob, Lynn, Morgans (prepare targeted questions for each of the below speakers)-Q&A session**
 - i. Heckenlively -WB, others (10mins)
 - ii. Adamus: WB/IHC (10mins)
 - iii. Chan: IHC /ELISA (10mins)
addressing the issues below
Standardization
 1. Reproducibility
 2. Concordance between labs

- 3. Dilution (IHC retinal tissue: animal vs human)
- iv. **Testing Strategies for the Identification of Antiretinal Antibodies John Hooks and Barbara Detrick (10mins)**
 - a. **Consensus voting for ARA testing (most reliable methods in order)**

9. 2:30-3:30pm: Future directions:

- a. Towards mechanistic studies (30mins)
 - i. B-cell assays: Phil McCoy (15 mins)
 - ii. Epigenetics: Lai Wei (15 mins)
 - 1. What other mechanistic studies should we be doing: reliable bioassays, assessing pathogenicity of antibodies in npAIR

- b. Towards clinical trials (15-20mins)
 - i. Results of Rituximab trial (Nida Sen) (5mins)
 - ii. Is randomization possible
 - iii. Is placebo (or at least single agent) fair? Clinical equipoise
 - iv. Registry
 - 1. **Consensus voting (randomized trials with or without placebo, natural history study with registry, priority?)**