MEETING NOTES FROM THE 45TH ANNUAL ARDS MEETING

Continuing our coverage of the 45th annual meeting of the Aspen Retinal Detachment Society (ARDS), Retina Today *is delighted to offer summaries of the lectures presented by Gregg T. Kokame, MD, and Debra A. Goldstein, MD.*

In "Combination Therapy for PCV and CNVM," Daniel Learned, MD, reviews Dr. Kokame's presentation on polypoidal choroidal vasculopathy and choroidal neovascular membranes, examining different cases addressed during the talk and highlighting the importance of combination therapies. Furthermore, he provides background on the PLANET and EVEREST studies and their potential influence in the field.

In "Infectious Posterior Uveitis," Retina Today's *senior editor, Michael Jones, provides an overview of Dr. Goldstein's first ARDS lecture, underscoring her application of Hickam's dictum in a case of infectious retinitis and discussing other uveitides for which retina specialists should be on the lookout in practice.*

—Timothy G. Murray, MD, MBA

Combination Therapy for PCV and CNVM

A comparison between two clinical studies provides insights on the treatment of PCV and CNVM.

By Daniel Learned, MD

Gregg T. Kokame, MD, gave an overview of studies looking at treatment patterns for the neovascular variant known as polypoidal choroidal vasculopathy (PCV). He also reviewed the characteristics of types 1, 2, and 3 choroidal neovascular membranes (CNVMs), first described by J. Donald M. Gass, MD.

Dr. Kokame presented three cases, showing each type of CNVM, and asked attendees how each would be treated. The consensus was that, for any CNVM type, intravitreal injection of an anti-VEGF agent would be the preferred treatment. His point was that any of these could be treated with anti-VEGF therapy, and differentiating them does not change the treatment plan.

Dr. Kokame then presented a case of PCV-related CNVM. The patient's visual acuity was 20/400 with acute vision loss. It improved to 20/50 and fluid resolved after photodynamic therapy (PDT) alone. Dr. Kokame also pointed out that, although it is not critical to differentiate between type 1, 2, or 3 CNVM, it is important to differentiate polypoidal variants because the treatments may be different.

ANTI-VEGF THERAPY IN PCV

According to Dr. Kokame, anti-VEGF therapy "is effective in decreasing leaking and bleeding but less effective in anatomical closure of polyps." This was shown in the EVEREST I trial, he noted. In further discussion, Joan W. Miller, MD, commented that she felt the reason that anti-VEGF therapy may not close polyps in PCV is that, if there is less blood flow through polyps, it is harder for the anti-VEGF agent to shut them down.

PLANET STUDY

Dr. Kokame presented data from the PLANET study in patients with PCV. This was a global, randomized, sham-controlled phase 3b/4 study at 62 sites comparing the safety and efficacy of aflibercept (Eylea, Regeneron) monotherapy versus a combination of aflibercept and PDT in the treatment of patients with PCV. He explained that because there was no PDT-only group, the study was not useful for examining whether PDT alone would work effectively against PCV, but the study did assess the benefit of monotherapy with aflibercept. The treatment plan was monthly injections of 2 mg aflibercept for 3 months, then every 8 weeks for the first year. This was followed by treat-and-extend versus interval treatment after year 1. Similar responses were seen in both arms, with a 10-letter increase.

EVEREST STUDIES

Dr. Kokame also reviewed results of EVEREST I and EVEREST II, and then extrapolated interesting comparisons between the EVEREST and PLANET studies. EVEREST I was the first to look at ranibizumab (Lucentis, Genentech) alone versus the combination of ranibizumab and PDT in patients with PCV, but the duration was only 6 months. The most valuable information from the study, according to Dr. Kokame, was that polyps were more likely to regress with PDT. The problem was the short length of the study.

The design of EVEREST II was similar to that of EVEREST I, examining ranibizumab alone and in combination with PDT, but the length was 24 months. At the time of Dr. Kokame's presentation, 12-month data was available. In EVEREST II, the combination group was treated with PDT initially, followed by 3 months of ranibizumab with a PRN regimen afterward. Repeat PDT could be applied for leakage. The ranibizumab group received a similar schedule, but without PDT.

In the combined group, 61% of eyes had only one PDT treatment, and 90% had two or fewer. Visual acuity results were better in

TABLE. RECOMMENDED TREATMENT OF PCV

Disease State	Treatment
Asymptomatic (50% of PCV)	No treatment recommended
Extra-Foveal Active Leakage	Macular laser or PDT
Sub-Foveal Active Leakage	VA 20/40 or better: anti-VEGF therapy
	VA < 20/40: consider combination treatment of PDT with anti-VEGF therapy
	Dense hemorrhage: anti-VEGF therapy

Abbreviations: PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; VA, visual acuity

the combined group (8 vs. 5 letters gained), central thickness was decreased more in the PDT group, and choroidal thickness and treatment exposure to ranibizumab were lower in the combined group (four vs. seven injections) compared with the ranibizumab-alone group. All primary endpoints were met, demonstrating that combination therapy was superior to ranibizumab monotherapy in improving 12-month visual outcomes, achieving complete polyp regression, and requiring fewer ranibizumab treatments.

COMPARING PLANET AND EVEREST

Dr. Kokame noted that, looking at the monotherapy aflibercept group in PLANET and the monotherapy ranibizumab group in EVEREST II, it appears that aflibercept may do better in this setting—with a gain of 10.7 letters for aflibercept compared with 5 letters for ranibizumab. Dr. Kokame referred to an animal study in Germany, which showed that ranibizumab was passively transported in between retinal pigment epithelium cells down a diffusion gradient, whereas aflibercept was actively transported to the retinal pigment epithelial spaces through intracellular spaces. Potentially, the type 1 CNVM would be better accessed by aflibercept because of its ability to be actively transported through intracellular spaces, resulting in better visual results for patients.

SUMMARY

There is growing recognition that PCV is a frequent cause of CNVM. The diagnosis is critical because in this setting the best treatment regimen may be different from other causes of CNVM. PDT should be considered for these patients, alone or in combination with anti-VEGF treatment. A comparison of the EVEREST and PLANET studies suggests that aflibercept may be a better choice, given its improved visual outcomes compared with those of ranibizumab. See the Table above for Dr. Kokame's treatment recommendations.

Infectious Posterior Uveitis

The challenges of identifying uveitis as a retina specialist.

By Michael Jones, Senior Editor

Debra A. Goldstein, MD, delivered her debut ARDS lectures at this year's ARDS meeting. Her first presentation, summarized below, addressed the importance of understanding the different infectious posterior uveitis diagnoses. During her talk, Dr. Goldstein discussed multiple cases from her own experience in the field as examples of challenging or missed uveitis diagnoses.

OCCAM'S RAZOR VS. HICKAM'S DICTUM

As many ophthalmology practices do not have a designated uveitis specialist, patients with retinitis often fall under the purview of the retina specialist.

Dr. Goldstein's first case example was a 68-year-old man who had received a primary vitreoretinal lymphoma diagnosis from another physician and presented to her with floaters and decreased vision (20/70 in the right eye [OD]; 20/20 in the left eye [OS]). After an examination, she realized that sarcoid uveitis was the more likely diagnosis, which was confirmed with testing. The patient was treated and recovered, but was lost to follow-up after 1 year due to the commute. A few years later, the patient again began to experience floaters OD and, based on his history, was diagnosed with a recurrence of sarcoid uveitis by another physician. He returned to Dr. Goldstein for a second opinion regarding a planned intravitreal steroid implant injection. This time, there were new findings consistent with herpetic retinitis, confirmed as secondary to varicella zoster on polymerase chain reaction (PCR) testing of an aqueous sample.

In medical school, doctors are taught Occam's razor, which states, "Plurality ought never be posed without necessity."[1] In other words, try to make everything fit one diagnosis. Dr. Goldstein explained her second diagnosis for this patient by citing Hickam's dictum, which states, "Patients can have as many diseases as they damn well please."[2] Even in patients with known underlying noninfectious uveitis, infectious retinitis may still develop.

In her second case, Dr. Goldstein discussed an immunosuppressed 71-year-old man with end-stage myelofibrosis. He was initially diagnosed with new onset intermediate uveitis and started on oral prednisone. Noting that, "A 71-year-old man with end-stage systemic disease who's being immunosuppressed does not get new noninfectious uveitis, period," Dr. Goldstein reexamined and diagnosed the patient with active toxoplasmic retinochoroiditis. She advised the ARDS attendees to assume that all retinitis is infectious until proven otherwise.

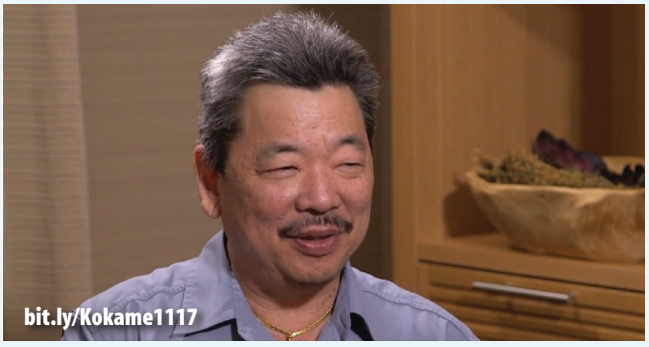
TOXOPLASMOSIS AND OTHER UVEITIDES

Toxoplasmosis is the most common cause of posterior uveitis in patients with normal immunity. According to Dr. Goldstein, it is not a diagnosis that is made based on blood tests, as a large percentage of individuals around the world have positive serology for toxoplasmosis. Instead, it is a clinical diagnosis with the option to confirm via PCR testing from ocular fluids. She also pointed out the importance of a full eye examination due to the common mistake of diagnosing anterior uveitis without properly inspecting the retina.

A myth about toxoplasmosis is that the disease is largely congenital when in fact the majority of disease is actually acquired postnasally. Dr. Goldstein discussed two patients with

WATCH IT NOW

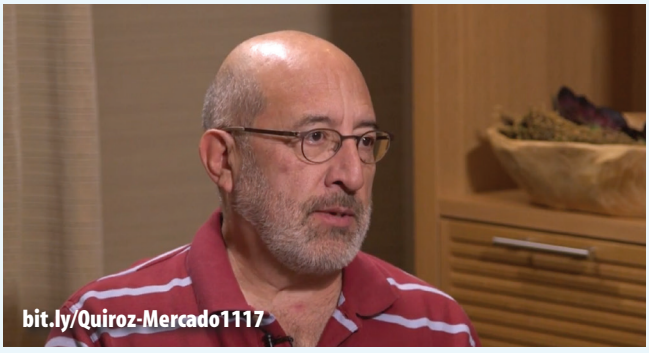
Polypoidal Choroidal Vasculopathy



Gregg T. Kokame, MD, joins Timothy G. Murray, MD, MBA, to discuss his talk on PCV. Dr. Kokame examines the importance of properly diagnosing this disease and the challenges in imaging these patients. Additionally, he addresses the role of PDT and anti-VEGF agents in the management of patients with PCV, reviewing the results of the EVEREST and PLANET studies.

WATCH IT NOW

Reoperations in Vitreoretinal Surgery



Hugo Quiroz-Mercado, MD, provides Timothy G. Murray, MD, MBA, an overview of his presentation on how the analysis of surgical procedures may reveal patterns in patients who require return visits to the OR. He reviews the importance of performing office-based procedures after OR complications as an alternative to OR reentry. Specifically, Dr. Quiroz-Mercado notes the value of performing an in-office air-fluid exchange for patients with retinal detachments and those post vitrectomy.

recurrent toxoplasmosis, followed by three patients with newly acquired toxoplasmosis. The patients with newly acquired disease all had active white patches of retinitis with no adjacent scars of old lesions. She also explained that, in an immune-compromised host, toxoplasmosis can also look like acute retinal necrosis (ARN). If treating toxoplasmosis with intravitreal injections of antibiotic and corticosteroid, Dr. Goldstein warned to refrain from using triamcinolone due to its long half-life in the eye.

Dr. Goldstein also discussed other causes of retinal infection, specifically herpes viruses (ARN and progressive outer retinal necrosis), diffuse unilateral subacute neuroretinitis, and Bartonella. She considered the consequences of diagnosing and treating these diseases, noting the importance of reevaluating a diagnosis if the disease is not responding as expected.

THE GREAT IMITATOR

Dr. Goldstein wrapped up her presentation with her self-confessed "favorite disease." As a uveitis specialist, much of her work is dedicated to managing diseases with no cure, but syphilis typically requires just 14 days of intravenous penicillin. She recited the famous William Osler quote: "The physician who knows syphilis knows medicine,"[3] and gave background on the disease and its progression in Europe.

According to Dr. Goldstein, anyone who has "ever had sex or been born" is at risk for syphilis, so it should be considered in every uveitis patient. Because sexually transmitted diseases travel in packs, anyone testing positive for syphilis should also be tested for HIV. She discussed four different patients presenting with different phenotypes, all of whom tested positive for syphilis; three were also found to be HIV positive.

SUMMARY

It is important for retina specialists to be able to recognize clinical features that suggest an infectious cause for uveitis. Dr. Goldstein stressed that it is a fallacy that all uveitis is treated with steroids and urged the audience to always keep infection in the differential diagnosis. ■

1. Wardrop D. Ockham's razor: sharpen or re-sheathe? *J R Soc Med*. 2008;101(2):50-51.
2. Borden N, Linklater D. Hickam's Dictum. *West J Emerg Med*. 2013;14(2):164.
3. Shockman S, Buescher LS, Stone SP. Syphilis in the United States. *Clin Dermatol*. 2014;32(2):213-218.

Daniel Learned, MD
- vitreoretinal fellow, Massachusetts Eye and Ear, Boston, Mass.
- financial interest: none acknowledged
- daniel.learned@gmail.com