

ASSESSING UVEITIS: BEYOND VITREOUS HAZE

A new, composite approach is needed.

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The presentations of uveitis are as varied as the brands of artificial tears at your local drug store. A case of panuveitis can just as easily present with choroidal thickening and headaches as it can with 4+ cell, 2+ vitreous

haze, and macular edema. The myriad presentations of even a single entity of uveitis, such as sarcoid uveitis, makes uveitis difficult to diagnose and manage, as each case must be evaluated and followed by its particular attributes. Treatment may be as straightforward as using local topical steroid formulations, or as involved as placing patients on long-term intravenous immunotherapy in addition to longer-acting local corticosteroids.

Given the diversity of diseases and presentations of uveitis, there are a number of parameters by which patients are assessed. Certainly, it is important to assess, record, and follow anterior chamber and vitreous cavity cells, as well as vitreous haze. However, given our increasing capability to image the eye, macular edema, the extent of retinal vasculitis, autofluorescence imaging, and choroidal thickening are also important measures of disease activity. Additionally, it is vital to assess the patient's symptoms, as a complaint of photopsia can indicate ongoing, uncontrolled disease activity.

GETTING ON THE SAME PAGE

This variability, along with the low prevalence of uveitis, makes it a difficult entity to study. This is all the more important in this day and age, as more localized, less toxic therapies are being developed for the treatment of our patients. Not long ago, a group of leading uveitis specialists gathered to discuss the various ways we describe our patients, in an effort to foster better communication about our cases to one another so that we can more meaningfully learn from one another. This initiative led to the Standardization of Uveitis Nomenclature, which has enabled better disease classification and an improved ability to teach and communicate with one another.¹

However, there were unforeseen consequences to this

effort as well. Given the difficulty of describing various posterior findings of uveitis and the relative infancy of ocular imaging, a consensus could not be achieved on the quantification of many posterior parameters beyond vitreous haze (Figure). This, unfortunately, has led to the over-reliance on vitreous haze as a marker of disease activity, especially in clinical trials regarding intermediate, posterior, and panuveitis. Vitreous haze has become the primary surrogate endpoint for these types of uveitis as far as the US Food and Drug Administration is concerned. Most ophthalmologists are aware of cases in which vitreous haze was not the primary feature of disease, and they understand how unreliable vitreous haze can be in this regard.

The inherent variability in measurement of vitreous haze also makes it a problematic endpoint. The grading of vitreous haze is based on comparison of indirect ophthalmoscopy with a series of photographs produced from a single image with diffusion filters by the National Eye Institute.² This leads to a somewhat subjective measure with inter-observer variability. In addition, grading may not correlate well with disease activity, especially at the lower end of the haze spectrum. The scale that is used to grade vitreous haze is not a truly continuous scale, but nevertheless the assigned ordinal values are used that way in clinical studies, with a 2-step reduction indicating meaningful change. Certainly, an increase from a 6-step to a 9-step photographic scale would be an additional step (or three) forward, if you



AT A GLANCE

- The presentation of uveitis is highly variable.
- The standard means of assessment, vitreous haze, is subjective and may not correlate with disease activity.
- A composite scoring system, as has been used in some investigator-initiated clinical trials, may allow improved communication among specialists and facilitate development of new therapies.

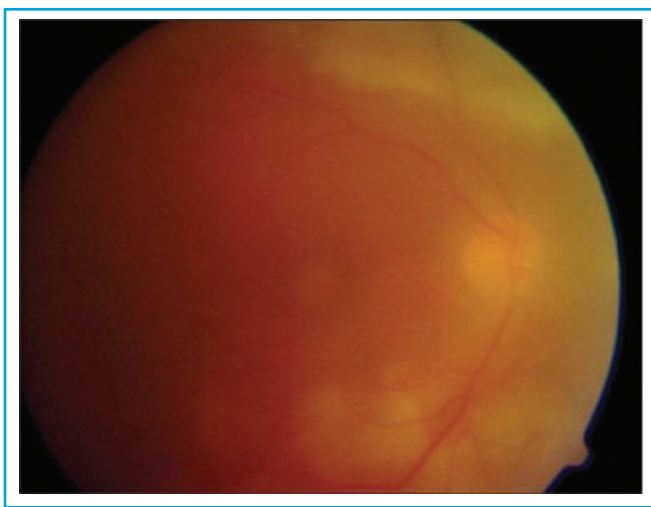


Figure. Although the US Food and Drug Administration relies on vitreous haze as the primary surrogate endpoint for uveitis, this clinical finding is not always the primary feature of the condition and is thus an unreliable sign. The 1 to 2+ vitreous haze in this image is so borderline that different clinicians could easily interpret it differently.

will pardon the pun.³ In a study using this expanded scale, not only was better interobserver agreement demonstrated, but the authors also reported that using the alternative scale would double the number of patients eligible for participation in clinical trials.^{4,5}

MEASUREMENT BY COMPOSITE SYSTEM

Even the way vitreous haze is measured should be reconsidered. In practice, vitreous haze does not command the level of importance it does in clinical studies. Cases are judged by all the presenting features, and the composite of this data forms the clinical vignette that we treat. Certainly, vitreous haze can be significant, but it can also be an asymptomatic, relatively minor feature that may represent chronic damage more so than current disease activity.

More objective measures are needed, and several are being evaluated. Use of optical coherence tomography (OCT) to measure haze is being studied, as well as enhanced-depth imaging OCT and widefield angiography. Still, each of these will have limitations of variability and may not correlate with true clinical activity.

Each single measure suffers many of the same deficiencies; however, taken together, they become a powerful way to monitor and study disease. To that end, perhaps, a composite score of the various manifestations of uveitis would be more helpful, not only for communication among retina specialists, but also for studying uveitis with the aim of developing better therapies with fewer side effects in the future. This type of composite system is used in other complex disease entities, such as thyroid eye disease, for which

the Clinical Activity Score⁶ and other indexes are used to assess patients.

In fact, a multifactorial system has been used in a single-center prospective study evaluating the efficacy of infliximab (Remicade, Janssen Biotech) in refractory uveitis. A composite clinical endpoint of visual acuity, control of intraocular inflammation, ability to taper concomitant medication therapy, and improvement in inflammatory signs on fluorescein angiography and/or OCT was established and used in this study⁷ as well as in a second multicenter study evaluating adalimumab (Humira, AbbVie).⁸ In the use of this scale, a grading of success required improvement in at least one of the four subcomponents and worsening in none.

TIME TO MOVE BEYOND VITREOUS HAZE

Given our growing ability to characterize and measure disease, a composite system makes sense, and the use of such a system must be thought through, especially for a disease state as heterogeneous as uveitis. Certainly it is time to rethink the role of vitreous haze in the evaluation of intermediate, posterior, and panuveitis, as our ability to evaluate the eye has advanced past use of this sole measure. This will be important not only in the evaluation of our patients, but also in facilitating communication among specialists and in helping to make the evaluation of new treatments easier, more reliable, and more accurate. ■

1. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):509-516.
2. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology.* 1985;92(4):467-471.
3. Davis JL, Madow B, Cornett J, et al. Scale for photographic grading of vitreous haze in uveitis. *Am J Ophthalmol.* 2010;150(5):637-641.
4. Madow B, Galor A, Feuer WJ, et al. Validation of a photographic vitreous haze grading technique for clinical trials in uveitis. *Am J Ophthalmol.* 2011;152(2):170-176.
5. Hornbeak DM, Payal A, Pistilli M, et al. Interobserver agreement in clinical grading of vitreous haze using alternative grading scales. *Ophthalmology.* 2014;121(8):1643-1648.
6. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol (Oxf).* 1997;47(1):9-14.
7. Suhler EB, Smith JR, Wertheim MS, et al. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol.* 2005;123(7):903-912.
8. Suhler EB, Lowder CY, Goldstein DA, et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. *Br J Ophthalmol.* 2013;97(4):481-486.

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