Through the eyes of an ocular immunologist: The interdisciplinary ophthalmology-rheumatology approach

Over the last 20 years, our understanding of uveitis has deepened, resulting in extraordinary advances in the management of these diseases. The most important of these advances include terminology standardization, enhanced diagnostic techniques, and refined treatment strategies that highlight the importance of interdisciplinary collaboration to improving patient outcomes and well-being.

Regarding advances in terminology, the Standardization of Uveitis Nomenclature Working Group's classification has been essential to promoting effective communication between specialists and researchers.[1] Terminology standardization guarantees a uniform interpretation of clinical signs, which have been proven to be important markers that are paramount to accurate diagnosis and thus influence therapy choices and prognosis evaluations.

For example, the term papilledema describes the swelling of the optic disc caused by increased intracranial pressure. It is a bilateral condition that should be taken seriously since it may be an indication of more severe issues such as brain tumor, hemorrhage, or idiopathic intracranial hypertension. In contrast, papillitis refers to an inflammation of the optic nerve. The former requires prompt investigation to find and solve the cause of high intracranial pressure; the latter may require immunosuppressive drugs or other specific therapies. Imprecise language can result in misdiagnosis, useless therapies, and even possibly dangerous outcomes for the patient.

Another scenario is that while the differentiation between granulomatous and nongranulomatous uveitis is based on clinical findings obtained on a slit-lamp examination, the term granulomatous is based on the histological characterization of the tissue.[2] Ocular immunologists use these now-standardized terms as clinical tools to classify diseases, assigning them to a subcategory of a group of uveitis that share common characteristics and that respond to a specific treatment.

An important step toward a better understanding and improved management of uveitis has been the establishment of precise classification criteria, revised and approved by globally recognized study groups such as the International Workshop on Ocular Sarcoidosis (IWOS, Tokyo, 2006, formed to address the recurrent problem of diagnosing ocular sarcoidosis)[3] and the Collaborative Ocular Tuberculosis Study (COTS, 2015, San Francisco).[4] The COTS has outlined the differences in the frequency of presentation and in some phenotypes of ocular tuberculosis depending on the latitudes of the world considered; for example, serpiginous choroiditis is more frequent in Asia than in the western countries. These criteria not only streamline diagnosis but also pave the way for tailored therapeutic approaches. These study groups have ensured that we now consider certain forms of uveitis as organ pathologies; ocular sarcoidosis, for example, was previously referred to systemic sarcoidosis. These classification criteria have therefore become increasingly important.

A further representative case is the diagnostic criteria for Behçet's disease,[5] which refer to uveitis as a diagnostic criterion in generic terms, i.e., it is not specified as nongranulomatous uveitis. Therefore, those who have clinical skills must interpret that only nongranulomatous uveitis is part of Behçet's criteria for disease classification. Otherwise, additional forms of uveitis that do not fit Behçet's clinical picture would also be included if one were to base their diagnosis only on the stated diagnostic criteria.

For retinal vasculitis, instead, there is currently no widely acknowledged classification system, although the disease has been categorized by etiology (infectious versus noninfectious), vascular caliber (large, medium, or small vessel disease), and clinical appearance (occlusive or nonocclusive).[6] It must be clarified that the term vasculitic eye involvement is not limited to retinal vasculitis. The term "ocular vasculitis" should encompass all ocular and periocular lesions caused by this process, including episcleritis, scleritis, peripheral ulcerative keratitis, choroidal and optic nerve vasculitis as well as orbital and adnexal lesions.[7]

Regarding the role of technology in the diagnosis and monitoring of ocular inflammation disorders, advances in multimodal imaging modalities, including optical coherence tomography (OCT) and laser flare photometry as well as ultrawide-field fluorescein and indocyanine green angiography, have benefitted patients tremendously. For example, juvenile idiopathic arthritis-related uveitis is no longer as threatening as it once was, thanks to biologic treatments (such as anti-tumor necrosis factor-α agents) and precise monitoring with laser flare photometry and other methods, which help preserve vision. However, proficiency in sophisticated diagnostic methods such as fundus photography, OCT, and genetic testing is required to achieve diagnostic accuracy and treatment planning.

However, while cutting-edge diagnostic devices have revolutionized patient management, and their use during the clinical examination for suspected uveitis is fundamental, it is important to beware of the risk of hyposkillia, i.e., a physician's reduced or lack of clinical skills due to an excessive dependence on modern medical technology and inadequate practical training. This decrease in practical medical skills can lead to unnecessary or excessive tests.

To illustrate hyposkillia in ophthalmology, when examining a patient with a clinical picture compatible with herpetic uveitis who is also incidentally HLA-B27 positive, the ophthalmologist must not be misled by this latter fact but stick to the diagnostic suspicion based on the clinical evaluation.

By addressing hyposkillia, the medical community can reduce unnecessary testing, thereby enhancing patient care.[8]

The third most important advance in the understanding and management of uveitis is the interdisciplinary approach; a perfect illustration of its value is the current management of Behçet's disease. Because Behçet's disease affects the skin, mucous membranes, joints, eyes, arteries, veins, nervous system, and gastrointestinal tract, among other organs and systems, optimal patient management necessitates the involvement of rheumatologists, ophthalmologists, dermatologists, and neurologists. In 2008, the first European League Against Rheumatism published their guidelines for managing Behçet's disease, which were well received by the entire medical community.[9]

A study by Olivieri *et al*. provides a compelling example of the value of multidisciplinary collaboration. The aim of that study was to standardize red flags for referral by both rheumatologists and ophthalmologists by means of a Delphi consensus for the management of rheumatic diseases with ocular involvement.[10,11] The Delphi survey involved Italian ophthalmologists and rheumatologists and consisted of three in-person sessions and two rounds of anonymous voting. Collaboration between the two specialties resulted in enhanced guidelines and consensus for patient referrals, thus confirming the importance of the constructive multidisciplinary approach introduced by Buzio *et al*.[11]

The value of teamwork is fully illustrated in the study in this special issue by Khan *et al*.[12,13] on HLA-B27-associated uveitis, which highlights the complex interactions between genetic predisposition and systemic therapeutic response. HLA-B27 represents the major genetic factor associated with acute anterior uveitis (AAU) in spondyloarthritis, and AAU is significantly more common in HLA-B27-positive than in HLA-B27-negative patients with ankylosing spondylitis.[12,13] To further emphasize this holistic perspective, pioneering studies such as that by Calin and Fries[14] have shed light on the intricate immunological mechanisms underlying uveitis. Their work, in fact, suggested that intestinal bacterial infections may trigger uveitis recurrence in HLA-B27-positive patients.

In terms of therapy, collaborating with specialists in other fields emphasizes the importance of adhering to classification criteria for diagnosis (e.g. the crucial role of the Chapel-Hill classification of vasculitis).

Moreover, it is important to minimize corticosteroid-related adverse effects like osteoporosis but also ensure the appropriate use of cortisone-sparing drugs because it is not advisable to combine two antimetabolite medications; however, an antimetabolite can be coupled with a biologic medication.

To provide their patients with "total" care, ocular immunologists must abandon the traditional approach to diagnosis and management, which aims to identify and cure a specific organ-associated disorder, as ophthalmologists may sometimes do. According to Professor Italo Portioli, an inspiring figure and our mentor, ocular immunologists must conduct "brave incursions" into other disciplines and fields of interest to discuss clinical cases with those specialists, request diagnostic investigations, and prescribe the best treatment for the patient's overall well-being.

A "brave incursion" has also been the introduction of molecular biology into clinical practice. While conducting a thorough clinical examination is the foundation of diagnosis, molecular biology increases specificity in diagnosing uveitis. "Having biologists at your side" has considerable implications;[15-17] if the cytokines are identified and studied, the pathology is better understood, allowing physicians to prescribe personalized drugs for each patient's specific pathology.

However, there are other things to take into consideration in terms of pathogenesis which will determine therapy. For example, the indirect evidence of the efficacy of anti-CD20-mediated B-cell depletion in treating autoimmune diseases supports an important role for B-cells in the development and propagation of these diseases. In clinical practice, the good response after rituximab therapy suggests an important role of B-cells in the pathogenesis of chronic recurrent uveitis associated with Vogt–Koyanagi–Harada (VKH) disease.[18,19]

Other challenges include infectious uveitis and uveitis masquerade syndromes. In fact, an aqueous humor tap is now performed in the differential diagnosis of cytomegalovirus-associated uveitis, and vitreous sampling is now conducted to further investigate vitreoretinal lymphoma.[20,21]

One of the many valuable aspects of the interdisciplinary approach has been the introduction of new concepts such as microbiome and microbiota, which underscore the wider systemic implications of ocular inflammation. This in turn should encourage more research into the role of host-microbiome interactions in the pathophysiology of uveitis.

Additionally, it is currently recognized that uveitis and arthritis associated with HLA-B27 are probably caused by autoimmunity as well as by an immune reaction to the microbiome. Sarcoidosis is now considered as the underlying cause for a portion of individuals who were previously diagnosed with idiopathic uveitis. Furthermore, the term "retinal vasculitis," which often generates misunderstanding, in fact, seldom aligns with the definition of vasculitis found in the rheumatology literature, and its occurrence rarely suggests a systemic condition.[22]

Yet another concept borrowed from a different discipline is the therapeutic window of opportunity–the period following the onset of a disease during which appropriate treatment can significantly alter the disease's outcome and potentially lead to a cure. Widely recognized as crucial in rheumatology, particularly for the treatment of rheumatoid arthritis,[23] this concept can be applied to initial-onset acute VKH disease,

where prompt and appropriate treatment results in significantly improved disease outcomes as it can prevent both chronic progression and complications like sunset glow fundus.[24]

However, there is not always a perfect overlap of understanding between different fields. For example, vascular cuffing and sheathing are often associated with the presence of cells in the anterior chamber of the eye. While the Ophthalmologist recognizes these findings as indicators of vasculitis, the Rheumatologist may not prioritize them in their assessment, as they are primarily considered vascular-venous issues specific to Ophthalmology. On the contrary, arterial retinal vasculitis such as in Susac syndrome or Wegener's granulomatosis manifests with no inflammatory cells in the anterior chamber. Arterial vasculitis, very rare in ophthalmological practice, is the most common in the rheumatological field.[25]

One of the highest points of recent interdisciplinary collaboration, with ophthalmologists interacting with other specialties, embracing new concepts and technologies, and prioritizing patient-centered treatment, has been the introduction of therapies with biological drugs. This has entailed ophthalmologists' undergoing a training process as ophthalmologists have a surgical background and are not therefore accustomed to managing patients with an "internistic" approach. This is seen in ophthalmologists' participating in regular meetings with the rheumatologists, infectiologists, and neurologists in establishing diagnostic-therapeutic care pathways, a great model of interdisciplinary collaboration.

New generations of ocular immunologists are on the horizon and need to be trained according to the principles advocated so far. This includes receiving training in how to adopt and adapt to an interdisciplinary approach, illustrated by the concept of interstitial medicine. This idea acknowledges the interdependence of disease processes and thus promotes comprehensive, 360° patient care that goes beyond traditional boundaries among medical specialities.[26] Interstitial medicine contrasts with scientific medicine, where the physician isolates the disease, breaks it down, describes it, and understands it. Currently, however, because a mutually respectful partnership between medical specialists is not the norm, many ophthalmologists may be discouraged from taking an interest in uveitis, which absolutely requires an interdisciplinary approach to patient care.

In conclusion, what we have learned about uveitis over the past few decades and how we now manage these complex diseases highlight the revolutionary impact of terminology standardization, innovations in technology, and interdisciplinary cooperation. These factors have played a role in fostering patient centered care and, ultimately, in improving patients' well being and quality of life.

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Submitted: 03-Mar-2025
Accepted: 04-Mar-2025
Published: 24-Mar-2025

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Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/sjopt.sjopt_81_25

How to cite this article: Ragusa E, Salvarani C, Cimino L. Through the eyes of an ocular immunologist: The interdisciplinary ophthalmology-rheumatology approach. Saudi J Ophthalmol 2025;39:1-4.