

# THE STATE OF NONINFECTIOUS UVEITIS TODAY

**U**veitis describes a group of diseases that produces inflammation within the uveal tract, but also potentially the lens, retina, optic nerve and vitreous.<sup>1</sup> The disease is classified, depending on the location of the manifestation, as: anterior, intermediate, posterior or panuveitis.<sup>1</sup>

Uveitis may be idiopathic in nature or the consequence of immunologic, infectious or other issues occurring within the eye, or an inflammatory condition affecting other parts of the body.<sup>1</sup> Irrespective of causation, research has shown that, in uveitis, macrophages and activated effector T cells lead to ocular inflammation,<sup>2</sup> photoreceptor destruction<sup>2</sup> and blood barrier leakage.<sup>2</sup>

Noninfectious uveitis, in particular, also known as autoimmune or autoinflammatory uveitis, is a heterogeneous group of diseases characterized by noninfectious inflammation within the eye.<sup>3</sup>

## DISEASE ONSET & BURDEN

Development of uveitis can happen at any time, although the mean age of presentation from reported studies around the world is approximately 40 years.<sup>1</sup> Research estimates more than 2 million people worldwide have uve-

itis,<sup>4</sup> and reports reveal uveitis is responsible for 30,000 new cases of blindness in the United States every year.<sup>1</sup> While generally considered a rare condition, uveitis is a leading cause of visual disability and sight loss.<sup>5</sup> Despite significant advances in research and therapeutics, uveitis remains the third leading cause of blindness around the world.<sup>4</sup>

## DETECTION & DIAGNOSIS

Onset of noninfectious uveitis symptoms can develop rapidly and bilaterally, and may include blurred vision, floaters, eye pain or redness or photophobia.<sup>1</sup> A multifaceted approach is essential to quickly diagnose noninfectious uveitis. Diagnostic tools including a complete medical history, a detailed review of medical systems, systemic and ocular examinations, and a targeted laboratory investigation can assist the clinician.<sup>1</sup>

## CONVENTIONAL THERAPY

Once the patient has been diagnosed with noninfectious uveitis, some retinal physicians opt to refer the case to a specialist; however, an opportunity exists for the retinal physician to complete the cycle of care for these important patients. In gen-



Photo: David Callanan, MD

## Sarcooid panuveitis

eral, treatment of noninfectious uveitis aims to eliminate inflammation, alleviate pain, prevent further tissue damage and potentially restore associated vision loss.

**Topical corticosteroids** are often used as first-line therapy.<sup>3</sup> In the case of intermediate or posterior uveitis, however, periocular or intravitreal injection, or systemic administration often is necessary.<sup>3</sup> Another line of defense, oral immunosuppressive agents, may be recommended to treat longstanding cases or those that demonstrate bilateral involvement. However, limiting factors for these conventional treatments persist.

**Systemic corticosteroids** can yield adverse side effects ranging from weight gain accompanied by cushingoid features and skin striae, to psychiatric disturbances, cardiovascular

## Intersection of Noninfectious Uveitis & Ocular Immune Privilege

Researchers have established the eye as an immune-privileged site<sup>10</sup> that limits ocular inflammation, where scarring is likely to result in blindness.<sup>3</sup> An intraocular vascular bed of microanatomical barriers located in the anterior segment restricts the movement of leukocytes into the eye and forms what is commonly known as the “blood-ocular barriers.”<sup>3</sup>

Noninfectious uveitis is the result of failed ocular immune privilege.<sup>3</sup> In human patients and experimental models, the disease’s characteristic inflammation reveals a mixed intraocular infiltrate of leukocytes.<sup>3</sup> Studies conducted primarily in mouse autoimmune uveoretinitis (EAU) indicate a cell-mediated autoimmune response coordinated by T cell lymphocytes and macrophages,<sup>3</sup> which is directed against antigens normally confined to the retina.

At the same time, the eye contains immunomodulatory molecules that suppress immune responses and activate infiltrating lymphocytes and macrophages.<sup>3</sup> These molecules include, among others, transforming growth factor (TGF)- $\beta$  2, cytokines IL-10 and IL-1RA, macrophage migration inhibitory factor, and neuropeptides such as  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), vasoactive intestinal peptide, somatostatin and calcitonin gene-related peptides.<sup>3</sup>

Alternative therapies and those in development have focused on the therapeutic impact of manipulating T cell and macrophage involvement, and more recently, that of B cell lymphocytes.<sup>3</sup>

As noninfectious uveitis continues to needlessly rob the sight of millions of patients worldwide, these unique approaches are key strategies in the battle to halt this serious and potentially devastating disease

disease and bone pathology.<sup>3</sup> When delivered locally, these agents can precipitate cataract formation and/or elevate intraocular pressure.<sup>3</sup> If taken for extended periods, corticosteroids may irreversibly damage the optic nerve and lead to glaucoma.<sup>3</sup>

**Immunosuppressive drugs** represent a last resort for most patients, as they are not universally effective for uveitis with one in two patients failing to achieve adequate disease control.<sup>1,3</sup> However, for some patients with destructive ocular sequelae, immunosuppressive drugs are absolutely indicated and the choice of immunosuppressive drug and regimen should be individualized to each patient.<sup>1</sup>

**Biologic immunosuppressive drugs** are therapeutic agents that use biological techniques to target specific aspects of the immune system and inflammatory pathways.<sup>1</sup> They offer hope for patients nonresponsive to conventional immunosuppressive drugs;<sup>4</sup> yet, life-threatening side effects, such as serious infections, new autoimmune diseases, hypersensitivity reactions and malignancies, can occur.<sup>4</sup>

### A DIFFERENT APPROACH

Given that an imbalanced immune system can lead to persistent inflammation and tissue damage—and is the underlying mechanism of autoimmune diseases—another way to approach therapy relies on immune cell modulation, known to play an integral role in the inflammatory response.

Within the inflammatory response, two distinct phases exist:<sup>6</sup> activation and resolution. Activation triggers pro-inflammatory mediator production, neutrophil and monocyte migration, and antigen-presenting cell activity.<sup>6</sup> Resolution, on the other hand, involves anti-inflammatory mediator production, macrophage phagocytosis, and treg cell expansion—active processes offering a protective response for the body.<sup>6</sup>

The melanocortins (MCs) are a group of peptide hormones, or ligands, that count as family members adrenocorticotrophic hormone and several forms of melanocyte-stimulating hormone, such as  $\alpha$ -melanocyte-stimulating hormone.<sup>7</sup> Derived from pro-opiomelanocortin in the pituitary gland,<sup>7</sup> MCs exert their effect

on the inflammatory response by binding to and activating melanocortin receptors.<sup>7,8</sup> MCRs, which are reflected in a multitude of cells and tissues in the body, are active participants in ocular protection.<sup>8,9</sup> It is clear the MC system plays a vital role in maintaining immune homeostasis, inducing immune tolerance, suppressing inflammation and promoting retinal cell survival. ■

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