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Intraocular Inflammation in Autoimmune Diseases

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BACKGROUND The uveal tract represents the vascular organ of the eye. In addition to providing most of the blood supply to the intraocular structures, it acts as a conduit for immune cells, particularly lymphocytes, to enter the eye. Consequently, the uveal tract is represented in many intraocular inflammatory processes. Uveitis is probably a misnomer unless antigens within the uvea are the direct targets of the inflammatory process. A better term of the condition is "intraocular inflammation" (IOI).

OBJECTIVES To review the presence of IOI in autoimmune diseases, the immunopathogenic mechanisms leading to disease, and treatment.

METHODS We reviewed the English medical literature by using MEDLINE (1984-2003) employing the terms "uveitis," "intraocular inflammation," and "autoimmune diseases."

RESULTS An underlying autoimmune disease was identified in up to 40% of patients with IOI, and included spondyloarthropathies, Behçet's disease, sarcoidosis, juvenile chronic arthritis, Vogt-Koyanagi-Harada syndrome (an inflammatory syndrome including uveitis with dermatologic and neurologic manifestations), immune recovery syndrome, and uveitis with tubulointerstitial disease. The immunopathogenesis of IOI involves enhanced T-cell response. Recently, guidelines for the use of immunosuppressive drugs for inflammatory eye disease were established and include: corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, and chlorambucil. New therapies with limited experience include the tumor necrosis factor α inhibitors, interferon alfa, monoclonal antibodies against lymphocyte surface antigens, intravenous immunoglobulin (IVIG), and the intraocular delivery of immunosuppressive agents.

CONCLUSION An underlying autoimmune disease was identified in up to 40% of patients with IOI. Immunosuppressive drugs, biologic agents, and IVIG are employed for the treatment of IOI in autoimmune diseases.

KEYWORDS intraocular inflammation, uveitis, autoimmune disease, biologic agents

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Ocular involvement in autoimmmune diseases may be manifested essentially in all eye layers: the cornea, sclera, and uvea (1). Each of these may characteristically be associated with an underlying autoimmmune disorder. Corneal disease occurs in rheumatoid arthirits, systemic lupus erythematosus, progressive systemic sclerosis, and Wegener's granulomatosis. Scleritis is most often seen with rheumatoid arthritis or with vasculitis. The HLA B27 spondyloarthropathies, sarcoidosis, and, in children, juvenile chronic arthritis (JCA), are the most common autoimmune diseases presenting with uveitis (approximately 50% of patients) referred to a uveitis clinic (2). Conversely, uveitis also may occur in the context of autoimmune diseases, including inflammatory bowel disease (IBD), Behçet's disease, Vogt-Koyanagi-Harada (VKH) syndrome, and multiple sclerosis (2,3). Retinal vascular lesions are seen with disorders having either a vaso-occlusive component, such as systemic lupus erythematosus, or with 1 of the vasculitides.

The uveal tract, comprising the iris, ciliary body, and choroids, represents the vascular organ of the eye. In addition to providing most of the blood supply to the intraocular structures, it acts as a conduit for immune cells, particularly lymphocytes, to enter the eye. Consequently, the uveal tract is represented in many intraocular inflammatory processes, irrespective of which tissue or cell is the original target of the immune process. Therefore, what was previously considered to represent a specific clinical entity, ie, uveitis, is probably a misnomer unless antigens within the uvea are the direct targets of the inflammatory process. A better term of the condition is "intraocular inflammation" (IOI) (4).

Many cases of IOI represent the first manifestation of a systemic disease. Although 60% of IOI is idiopathic, an underlying systemic disease, often of an autoimmune origin, can be identified in up to 40% of patients with IOI (5). The transparency of the eye enables direct visualization of vasculopathic processes in small vessels. Moreover, angiographic imaging such as fluorescein angiography (FA) and indocyanine green (ICG) imaging make it possible to examine not only the appearance of small vessels and neighboring tissues in the retina or choroid, but also the functional properties of these vessels. Direct visualization of the vessels enables the ophthalmologist an in-depth evaluation of inflammatory processes, sometimes before substantial tissue damage occurs. It also may give the internist additional data as to the effect of therapy on stabilization versus progression of disease, using tools that may diagnose subtle changes that otherwise remain unnoticed.

Materials and Methods

We reviewed the relevant medical literature by the use of MEDLINE (1984-2003) employing the terms "uveitis," "intraocular inflammation," and "autoimmune diseases."

Results

Ophthalmic Symptoms and Signs

The most common symptoms of anterior IOI are blurred vision, photophobia, tearing, pain, and hyperemia. These are accompanied by pathologic processes such as migration of inflammatory cells into intraocular cavities; engorgement of intraocular vessels; or inflammatory infiltrates visible, for instance, as nodules on the iris and edema of sight-regulating tissues such as the retina or cornea (6). Blurred vision may the result of actual damage to ocular tissues, but may also be caused by shifts in refraction resulting from changes in lens position, hypotony, macular edema, or similar occurrences. Other possible causes of blurred vision include opacities in the visual axis by inflammatory cells, fibrin, or protein in the anterior chamber, or secondary cataract. Pain in IOI usually results from acute iritis (inflammation in the region of the iris), scleritis, or corneal damage. Elevated intraocular pressure, another cause of pain, may result from interruption of aqueous humor drainage. The pain associated with ciliary spasms in iritis may be referred over a large area served by the fifth cranial nerve. Photophobia and excessive tearing usually are present when inflammation involves the iris, cornea, or the ciliary body.

In intermediate IOI, vision impairment may be primarily caused by vitritis or chronic macular edema. However, floating opacities (the accumulation of cells and protein within the vitreous) in the visual field (floaters) may be the sole symptom. These eyes frequently are asymptomatic (2).

Visual symptoms of posterior IOI may be caused by involvement of the macula, affecting central vision, or choroidal and/or retinal infiltrates, hemorrhage or infarction, subretinal neovascularization, or associated vitritis. Inflammatory processes involving the retina also may extend into the vitreous (ie, retinitis with vitritis), causing floaters. Whereas acute IOI is always symptomatic, chronic IOI disease might be discovered on routine ophthalmologic examination in a patient without ocular symptoms.

Etiology of IOI

Discussion of all forms of IOI is beyond the scope of this article, so we will focus on forms of IOIs with frequent systemic consequences. The 2 major forms of IOIs are anterior-segment IOI, and posterior-segment IOI (7). In some cases, combined anterior- and posterior-segment IOI may occur (panuveitis), which sometimes represents progression in severity of one or the other primary forms (Table 1).

There are some typical ocular findings such as hypopyons, iris nodules, posterior synechia that are related to specific IOI entities (HLA B27–related syndromes, Behçet's syndrome, and sarcoidosis) (5,8). Nevertheless, the high degree of overlap of these phenomena in different IOI entities has reduced their diagnostic significance.

By far, the anterior chamber response is characteristic of autoimmune diseases, whereas the prevalence of infectious entities is higher in posterior IOI. The differential diagnosis of posterior IOI is long and conventionally grouped into 3 major pathologic categories, eg, autoimmune, infectious, and tumors. Within these groups, conditions may present with focal, multifocal, or diffuse involvement.

Immune recovery uveitis is an IOI occurring in individuals with human immunodeficiency virus infection receiving highly active antiretroviral therapy (HAART) and who have a

Table 1 Classification of IOI with Systemic Manifestations

Anterior IOIs	Onset	Laterality	Typical and demographics/systemic signs and symptoms, Type of KP
Spondyloarthropathy	Acute	Unilateral	Male, arthritis, rash, genital ulcers
IBD	Not specific		Female, gastrointestinal involvement
JCA	Chronic		Young female, arthritis
Behcet's disease	Acute	Unilateral	(see posterior IOI)
Intermediate IOIs			
IBD	Not specific		Female, gastrointestinal involvement
Pars planitis (idiopathic)	Chronic	Bilateral	Young-adult, occasionally patients develop multiple sclerosis
Posterior IOIs			
VKH syndrome	Acute		Adult, Asia, headaches, deafness, CSF pleocytosis, vitiligo, poliosis, alopecia.
Behçet's disease	Acute	Unilateral	Adult, arthritis, CSF pleocytosis, weakness, erythema nodosum, skin and nodules and rash, oral and genital ulcers
Pan IOIs			
Sarcoidosis	Chronic		Young-adult, deafness, erythema nodosum, skin nodules and rash, salivary gland and lymphoid enlargement, dyspnea, vasculitis, CSF pleocytosis*, psychosis*, granulomatous KP.

Abbreviations: KP, keratic precipitate; CSF, cerebrospinal fluid.
*Neurosarcoidosis is uncommon.

history of cytomegalovirus retinitis (9-11). The pathogenic mechanism represents an immune response against intraocular antigen(s) in a patient with restoration of the immune system resulting from HAART (9-11). On the other hand, VKH syndrome, or uveomeningitic syndrome, is a typical example of a T-cell–mediated autoimmune posterior-segment disease in which the melanocytes are the primary target of attack. Thus, there is involvement of the eyes, meninges, inner ear, and skin. Exudative retinal detachment is the hallmark of the syndrome, but systemic manifestations that include meningeal signs, alopecia, vitiligo, and hearing disturbance (12) are commonly seen in the complete form of the disease.

Panuveitis may follow a stormy or a slowly debilitating course. Usually, infectious pathogens, such as fungi and bacteria, lead to an acute, severe form of the disease, whereas autoimmune entities run a slower, yet resistant, pattern of disease progress.

Chronic IOIs can be characterized as either granulomatous or nongranulomatous. Nongranulomatous inflammations have a lymphocytic and plasma cell infiltrate, whereas granulomatous reactions also include epitheloid and giant cells. Although these features are of great pathologic significance, they have limited clinical value. Discrete granulomas are characteristic of sarcoidosis and tuberculosis, whereas diffuse granulomatous inflammation is seen in the VKH syndrome. However, the physician should be aware that the appearance of IOI as granulomatous or nongranulomatous might be related to the stage of the disease, the amount of presenting antigen, or the host state of immunocompetence.

Sarcoidosis can present in any location within the eye as either an acute or a more slowly progressive process. Bilateral involvement occurs in 80% of patients with sarcoidosis (13). Syphilis, said to be the "great pretender," also can cause several different forms of IOI, ranging from keratitis, anterior IOI, retinitis, and optic neuritis (14). Thus, systemic and laboratory findings are essential for accurate diagnosis of these 2 diseases. Interstitial nephritis can be associated with an iritis that is usually bilateral and acute in onset. Patients with this association are generally systemically ill, with symptoms that may include fever, anemia, abdominal pain, fatigue, azotemia, and pyuria (15).

Many cases of anterior IOIs are of unknown etiology and generally resolve within 6 weeks. These cases do not necessitate an in-depth evaluation, because the inflammation does not often recur (16).

Oligoarthritis and anterior or intermediate IOI commonly coexist in systemic diseases (Table 2). The most common form of anterior IOI is a self-limiting recurrent iritis or iridocyclitis, associated with the HLA-B27 haplotype in 50% of cases. The reported prevalence of anterior IOI in spondyloarthropathies is substantial and may reach 20% to 40% in ankylosing spondylitis or reactive arthritis, 7% in psoriatic arthritis, and 3% to 11% in IBD (2,17,18). In sarcoidosis, the frequency of anterior IOI may reach 32%, and in Behçet's disease and Kawasaki's disease, it may reach 66% and 78%, respectively (3).

Chronic anterior uveitis is less common than acute anterior uveitis and most frequently is encountered in seronegative JCA (19,20). This type of uveitis is termed "white eye" uveitis because of the paucity of symptoms, and thus, the visual consequences may be severe. In 6% to 20% of cases, the uveitis precedes the arthritis by at least 5 years. Unlike most forms of uveitis, detection of elevated antinuclear antibodies (ANA) can be informative (21). Factors associated with sight-threatening complications of uveitis in children with JCA include a chronic course, juvenile psoriatic arthropathy, diagnosis of uveitis before or at the time of arthritis onset, and symptomatic onset (22,23). Juvenile ankylosing spondylitis is associated with sudden-onset unilateral ante-

Table 2 Characteristics of Anterior IOI in Rheumatic Disease

Typical Presentation	Systemic Disease Association	Prevalence of Anterior IOI %
Acute, recurrent, and unilateral predominance	Ankylosing spondylitis	20-40
	Reactive arthritis	20
	Psoriatic arthritis	7
	IBD	3-11
	Late-onset JCA	25
Chronic granulomatous inflammation	Sarcoidosis	32
Chronic and bilateral	Early-onset JCA	53
Acute, bilateral, recurrent, may progress to chronic IOI	Behçet's syndrome	66

(continued)

rior uveitis. Systemic onset and polyarticular disease are rarely associated with uveitis. Recently, the HLA DQA1*0501 allele was found to be associated with different JCA groups/subgroups: oligoarticular type; polyarticular type; rheumatoid factor–negative; ANA-positive; and JCA with chronic anterior uveitis, probably suggesting a closer relationship of this locus with the immunogenetic background of JCA (24).

Immunopathogenesis of IOI

The known clinical observation that traumatic injury to 1 eye sometimes leads to a delayed ocular inflammation that is expressed in both the injured and its fellow, nontraumatized, contralateral eye was named "sympathetic ophthalmia" (25). This condition has led to the concept that autoimmune processes directed at tissue-restricted antigens of the eye play a major role in certain inflammatory conditions of the eye. Experimental autoimmune uveoretinitis (EAU) is an animal model for many types of IOIs in individuals with clinical and histologic similarities of sympathetic ophthalmia (26). Studies in animal models significantly help delineate the molecular mechanisms underlying IOI. Models of ocular autoimmune disease and ocular inflammation can be divided into 3 groups: 1) uveitis mediated through nonocular-derived antigens, 2) EAU, and 3) ocular, but nonretinal, antigen-derived autoimmune disease. Uveitis mediated through nonocular-derived antigens models include endotoxin-induced uveitis, cytokine-induced inflammation, and adjuvant-induced uveitis (27). The effects of endotoxin-induced uveitis are probably the result of the lipid moiety within the lipopolysaccharide molecule (27). EAU can be induced by retinal S-antigen (S-Ag), interphotoreceptor retinoid–binding protein (IRBP), rhodopsin, and other retinal proteins (27).

Experimental models have identified retinal S-Ag (28), IRBP (29), rhodopsin (30), and recoverin (31) to be "uveitogenic."

The study of models of ocular autoimmunity and of autoimmune uveitis in humans led to a shift in the perceived nature of immune privilege from 1 based on anatomic isolation of the eye to a more dynamic, active process of immune tolerance. The protective role of humoral immunity, the costimulatory function of B cells in EAU, and the influence of cytokines within the inflammatory cascade are well established (27). Another mechanism includes the modulation of the immune response, and in particular, the possible role of macrophages. Within the current paradigm, a major effector cell is the $CD4^+$ lymphocyte. Its maturation into a T-helper (Th)1 or Th2 phenotype process appears dependent on a number of exogenous factors, which, although genetically determined, can be manipulated before the disease onset. Activation of $CD4^+$ cells is dependent on presentation of immunoreactive peptide fragments. These fragments are well characterized in the Lewis rat for S-Ag and IRBP (27).

Mapping of the immunoreactivity to S-Ag recently was completed in uveitis patients. The amino acid sequences of S-Ag from bovine, human, murine, and rat retinas were deduced from cDNA sequencing and showed high homology (27,32-35). Cleavage fragments of S-Ag and synthetic peptides were used to identify domains involved in lymphocyte recognition, immunogenicity, and pathogenicity. In the Lewis rat, certain short amino acid sequences were capable of inducing EAU and proliferation of sensitized lymphocytes (36,37).

Evidence for Ocular Autoimmunity in Humans

Ocular privilege is not caused by antigen sequestration, but by an active down-regulation of a proinflammatory response. Thus, a response to antigen can be expected under in vitro culture conditions in normal individuals and frequently is observed. The intensity of this response distinguishes patients from normal individuals (28,29). Because EAU can be induced in so many different animal species, including the primate, it is temping to consider that retinal antigens are responsible for a variety of human uveitis conditions of unknown origin. EAU has a very polymorphic phenotype, manifesting itself as fulminant retinitis, granulomatous choroiditis, or segmental vasculitis, depending on the immunizing antigen, its dose, and the chosen animal model. Thus, it can mimic a wide variety of human inflammatory conditions and, as a model, is helpful in predicting the behavior of certain forms of clinical disease. So far, no causal link has been made between retinal autoantigens and human retinal inflammation, although retinal autoantigens probably are implicated at some point in the pathogenesis of a number of uveitic conditions. Over the years, a number of researchers have autoimmunized themselves with S-Ag or IRBP. None, with the possible exception of 1 individual, developed ocular sequelae (26).

Numerous authors reported positive lymphocyte stimulation responses with crude retinal extracts, S-antigen, IRBP,

and a host of other antigens. Cellular responsiveness to ocular antigens is augmented during active disease rather than remission, in diffuse forms of uveitis (panuveitis) rather than purely posterior ones, in subacute or chronic disease states rather than in acute self-limited disease, and after the disease has evolved for some time (27).

Several studies characterized the response to peptide determinants of S-Ag and IRBP in a variety of uveitis conditions (30) and ankylosing spondylitis (31). Lymphocyte responses to 40 overlapping peptides of human S-Ag were studied in a number of ocular inflammatory conditions. Behçet's disease and sarcoidosis patients gave the most frequent and consistent responses (38). A characteristic of all responding patient populations was the ability to recognize multiple determinants simultaneously (termed "determinant spread").

Strong HLA associations have been observed in many types of human uveitic diseases (39). Associations include HLA-B27 in acute anterior uveitis (40), HLA-B51 in Behçet's disease (41,42), and HLA-B44 in occlusive vasculitis (43). A recent study in Behçet's disease patients showed that those with active uveitis had a significant response to B27PD (a peptide derived from HLA-B27 with homology for HLA-B51) as compared with Behçet's disease patients without uveitis, or normal controls (44).

Sarcoidosis is associated with HLA-DRB1 or DRB3 (45), whereas the VKH syndrome has an association with HLA-DRB1* (46). A human T-cell line restricted to HLA DRB1*0405 derived from a Japanese VKH patient responded to a tyrosinase determinant EIWRDIDFAHE (aa 193-203) (47). This same tyrosinase-derived peptide can induce choroiditis in the Lewis rat (48). Autoantibodies to retinal antigens do not seem to play an active role in the induction phase of disease. Evidence for this is derived from various sources. The study of human pathologic specimens reveals the presence of infiltrating $CD4^+$, but not B, cells in the early phase of Behçet's disease (49) and sarcoidosis (50). The presence of circulating immune complexes in Behçet's disease is associated with a better prognosis or is a sign of good control on medication. No difference in levels of anti–retinal S-Ag and anti-IRBP antibodies was detected in the serum of patients and controls (51,52). Taken together, these findings suggest that antibodies in uveitis have a regulatory, or possibly even a protective, role. The presence of a sufficient level of antibodies may even prevent recurrences, but this remains to be demonstrated.

Both serum and intraocular fluids were studied by a number of investigators for evidence of immune activation in uveitis. Increased levels of inflammatory cytokines interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF) were detected in ocular fluids in a variety of uveitis conditions (53). Studies in serum samples are more difficult to interpret. Elevated circulating levels of intercellular adhesion molecule (ICAM)-1 in intermediate uveitis patients are indicative of an associated systemic illness or a predisposition for developing systemic manifestations shortly thereafter (54). In another study, no difference in circulating levels of soluble IL-2 receptors were observed when comparing patients with uveitis associated with a systemic illness, with patients who had uveitis of a purely ocular origin (55). A recent report in which patients were followed prospectively suggested an association between increased serum levels of macrophage inhibitory factor (MIF) and disease activity in Behçet's disease and in sarcoidosis (56). Lymphocytes infiltrating the vitreous and anterior segment were studied in a number of conditions and found to be predominantly of $CD4^+$ origin (55). Cloned $CD4^+$ anterior chamber lymphocytes were studied in the VKH syndrome and sarcoidosis patients (57); they produced mainly inflammatory cytokines. Some disease-specific variation in the pattern of secreted cytokines was observed, as well as a differential secretory response to immunomodulatory agents such as hydrocortisone and tacrolimus.

Circulating cells responding to S-Ag were estimated using 2 approaches and produced roughly the same result (58). For uveitis patients, S-Ag–responsive cells were in the range of 0 to $400/10^7$ circulating mononuclear cells, whereas for control subjects, it was about 0 to $4/10^7$ cells (28). A further question is whether the number of circulating cells changes in relation to disease activity. In 1 study, flow cytometry was used to demonstrate expansion of particular TCR V regions of peripheral blood T cells of Behçet's disease patients. Six of 8 patients developed at least 1 expansion in a follow-up period of up to 20 months. These expansions correlated with disease activity (59). Using a modified limiting dilution assay, the expansion of the pool of S-Ag reactive peripheral lymphocytes was demonstrated immediately following IOI in 3 Behçet's disease patients. The pool of responsive cells expanded up to 30 times over the preinflammatory level. This elevated pool persisted for up to 3 months before returning to the preinflammatory level (60).

Treatment Regimens for IOI

Determination of the proper therapy for patients with uveitis is difficult because of the lack of guidelines and the paucity of randomized, controlled, clinical trials. Treatment decisions should include the compartment of inflammation. Topical corticosteroid eye drops are reserved for anterior uveitis. However, children with JCA may benefit from therapy with methotrexate or cyclosporine, sparing the side effects of topical steroid treatment such as cataracts and elevated intraocular pressure (2). Periocular injections of steroid can be administered if the inflammation is unilateral. Because of their better penetration into posterior ocular tissues, injections should be considered in posterior IOIs, whereas topical drops usually are effective in anterior IOIs. In severe bilateral intermediate or posterior IOI, immunosuppressive therapy is indicated. The drug of choice is high-dose systemic corticosteroids, followed by slow tapering of dosage with or without the addition of another immunosuppressive, steroid-sparing agent such as methotrexate or cyclosporine (2,61).

Finally, some patients with chronic IOI have a lingering mild flare consisting of occasional leukocytes within the anterior chamber and vitreous cavity, without associated symptoms such as pain and red eye. These patients probably have a permanent alteration of iris vascular permeability; therefore, corticosteroids should be tapered with close follow-up,

rather than continuing prolonged topical steroids in an attempt to eliminate every sign of anterior chamber reaction.

Recently, guidelines for the use of immunosuppressive drugs for inflammatory eye disease were established and include corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, and chlorambucil (62). Azathioprine and/or cyclosporine are effective in the management of ocular inflammation in Behçet's disease' open-label trials suggest a high rate of clinical response (63). Sulfasalazine was reported to ameliorate the severity and prevent recurrences of anterior IOI associated with HLA B27 (64).

New therapies with limited experience in treating uveitis include the TNF inhibitors (65), interferon alfa (66), monoclonal antibodies against lymphocyte surface antigens (67-69), intravenous immunoglobulin (IVIG) (70), and the intraocular delivery of immunosuppressive agents (71).

Experimental Treatments

Oral tolerance had a beneficial role in immunomodulating both experimental and clinical autoimmune diseases (72-74), suggesting that this therapeutic approach might benefit patients with IOI. A phase I/ II randomized, clinical trial compared the oral administration of retinal antigens with placebo, in patients with IOI. Although not statistically significant, those assigned to receive retinal S-antigen were more likely to be tapered off their chronically administered systemic immunosuppressive therapy (75). Oral tolerance with an HLA-peptide mimicking retinal autoantigen as a treatment of autoimmune uveitis also has been investigated (76).

Reports indicate the clinical benefit of therapy with monoclonal antibodies targeted against lymphocyte surface antigens: CAMPATH-1H (humanized anti-CD52 antibody) (67), daclizumab (humanized anti–IL-2 receptor monoclonal antibody) (68), and humanized monoclonal anti-CD4 antibody (69).

IVIG was effective for refractory uveitis in an open-label, prospective study of 8 treatment-resistant uveitis patients. One half of the patients had substantial benefit over a median period of 11 months (70).

Intravitreal implants with slow release of corticosteroid or cyclosporine are under investigation. In 1 study, fluocinolone acetonide implants were inserted into 7 eyes of 5 uveitis patients. After an average of 10 months, all eyes were stabilized, without any evident inflammation (71).

Discussion

"Intraocular inflammation" has emerged as a more appropriate term than "uveitis," because it embraces the mechanisms of action in which the eye is a partner in autoimmune activation in up to 40% of cases. Thus, IOI is part of multisystemic diseases rather than being organ-specific. In the future, perhaps some of the 60% of idiopathic causes will prove to be autoimmune in nature. The autoimmune spectrum involving IOI includes predominantly T-cell–mediated disease. Interestingly, the humoral arm plays more of a protective, rather than a pathologic, role in these diseases. Therefore, the concept that the eye is an immune-privileged organ should be challenged. The major autoantigens are of ocular origin, supporting the notion that extraocular autoantigens are not dominant; rather, a faulty multisystem immune surveillance mechanism is involved. For the rheumatologist, ocular presentations and symptoms should always be taken seriously, and a link with autoimmune disease should be sought. Established therapy is immunosuppressive, and thus associated with toxic effects. The recent use of biologic agents may prove to be beneficial in the future. Intraocular administration of immunosuppressive agents also seems promising. Future studies will be aimed at identifying with more detail immunologic triggers of inflammation, and at better defining the interplay between effector and regulatory pathways both in the eye and in the systemic circulation. This will allow for better management of intraocular disease.

References

1. Hamideh F, Prete PE. Ophthalmologic manifestations of rheumatic diseases. Semin Arthritis Rheum 2001;30:217-41.
2. Smith JR, Rosenbaum JT. Management of uveitis: a rheumatologic perspective. Arthritis Rheum 2002;46:309-18.
3. Rosenbaum JT. Uveitis. Arch Intern Med 1989;149:1173-6.
4. Rosenbaum JT, Nozik RA. Uveitis: many diseases, one diagnosis. Am J Med 1985;79:545-7.
5. Forrester JV. Endogenous posterior uveitis. Br J Ophthalmol 1990;74: 620-3.
6. Bloch-Michel E, Nussenblatt RB. International Uveitis Study recommendations for the evaluation of intraocular inflammatory disease. Am J Ophthalmol 1987;234-5.
7. Duke-Elder S, Perkins ES. Diseases of the uveal tract. In: Duke Elder S (ed): Systems of Ophthalmology, vol 9, p 545 St Louis: CV Mosby, 1966.
8. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol 1996;80:332-6.
9. Robinson MR, Reed G, Csaky KG, Polis MA, Whitcup SM. Immune-recovery uveitis in patients with cytomegalovirus retinitis taking highly active antiretroviral therapy. Am J Ophthalmol 2000;130:49-56.
10. Holland GN. Immune recovery uveitis. Ocular Immunol Inflamm 1999;7:215-22.
11. Zegans ME, Walton RC, Holland GN, O'Donnell JJ, Jacobson MA, Margolis TP. Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. Am J Ophthalmol 1998;125:292-300.
12. Read RW. Vogt Koyanagi Harada syndrome. Ophthalmol Clin North Am 2002;3:333-41.
13. Jones NP. Sarcoidosis and uveitis. Ophthalmol Clin North Am 2002; 3:319-26.
14. Aldave AJ, King JA, Cunningham ET Jr. Ocular syphilis. Curr Opin Ophthalmol 2001;12:433-41.
15. Takemura T, Okada M, Hino S, Fukushima K, Yamamoto S, Miyazato H, et al. Course and outcome of tubulointerstitial nephritis and uveitis syndrome. Am J Kidney Dis 1999;34:1016-21.
16. Banares A, Jover JA, Fernandez-Gutierrez B, Benitez del Castillo JM, Garcia J, Vargas E, et al. Patterns of uveitis as a guide in making rheumatologic and immunologic diagnoses. Arthritis Rheum 1997;40:358-70.
17. Paiva ES, Macaluso DC, Edwards A, Rosenbaum JT. Characteristics of uveitis in patients with psoriatic arthritis. Ann Rheum Dis 2000;59:67-70.
18. Lyons JL, Rosenbaum JT. Uveitis associated with inflammatory bowel disease compared with uveitis associated with spondyloarthropathy. Arch Ophthalmol 1997;115:61-4.

19. Rothova A, van Veenedaal WG, Linssen A, Glasius E, Kijlstra A, de Jong PT. Clinical features of acute anterior uveitis. Am J Ophthalmol 1987; 103:137-45.
20. Kanski JJ. Uveitis in juvenile chronic arthritis: incidence, clinical features and prognosis. Eye 1988;2:641-5.
21. Murray P. Serum autoantibodies and uveitis. Br J Ophthalmol 1986; 70:266-8.
22. Cabral DA, Petty RE, Malleson PN, Ensworth S, McCormick AQ, Shroeder ML. Visual prognosis in children with chronic anterior uveitis and arthritis. J Rheumatol 1994;21:2370-5.
23. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol 2002;86:51-6.
24. Pratsidou-Gertsi P, Kanakoudi-Tsakalidou F, Spyropoulou M, Germenis A, Adam K, Taparkou A, et al. Nationwide collaborative study of HLA class II associations with distinct types of juvenile chronic arthritis (JCA) in Greece. Eur J Immunogenet 1999;26:299-310.
25. Sharp DC, Bell RA, Patterson E, Pinkerton RM. Sympathetic ophthalmia: histopathologic and fluorescein angiographic correlation. Arch Ophthalmol 1984;102:232-5.
26. Nussenblatt RB, Kuwabara T, de Monasterio FM, Wacker WB. S-antigen uveitis in primates: a new model for human disease. Arch Ophthalmol 1981;99:1090-2.
27. de Smet MD, Chan CC. Regulation of Ocular Inflammation—what experimental and human studies have taught us. Progress In Retinal and Eye Research 2001;20:761-97.
28. Bieganowska KD, Ausubel LJ, Modabber Y, Slovik E, Messersmith W, Hafler DA. Direct *ex vivo* analysis of activated, Fas-sensitive autoreactive T cells in human autoimmune disease. J Exp Med 1997;185:1585-94.
29. de Smet MD, Yamamoto JH, Mochizuki M, Gery I, Singh VK, Shinohara T, et al. Cellular immune responses of patients with uveitis to retinal antigens and their fragments. Am J Ophthalmol 1990;110:135-42.
30. Yamamoto JH, Minami M, Inaba G, Masuda K, Mochizuki M. Cellular autoimmunity to retinal specific antigens in patients with Behcet's disease. Br J Ophthalmol 1993;77:584-9.
31. Nityanand S, Singh VK, Shinohara T, Paul AK, Singh V, Agarwal PK, et al. Cellular immune response of patients with uveitis to peptide M, a retinal S-antigen fragment. J Clin Immunol 1993;13:352-8.
32. Shinohara T, Dietzschold B, Craft CM, Wistow G, Early JJ, Donoso LA, et al. Primary and secondary structure of bovine retinal S-antigen (48-kDa protein). Proc Natl Acad Sci U S A 1987;84:6975-9.
33. Yamaki K, Tsuda M, Shinohara T. The sequence of human retinal S-antigen reveals similarities with a-transducin. FEBS 1988;234:39-43.
34. Tsudu M, Syed M, Bugra K, Whelan JP, McGinnis JF, Shinohara T. Structural analysis of mouse S-antigen. Gene 1988;73:11-20.
35. Abe T, Shinohara T. S-Antigen from the rat retina and pineal gland have identical sequences. Exp Eye Res 1990;51:111-2.
36. de Smet MD, Bitar G, Roberge FG, Gery I, Nussenblatt RB. Human S-antigen: presence of multiple immunogenic and immunopathogenic sites in the Lewis rat. J Autoimmun 1993;6:587-99.
37. Gregerson DS, Merryman CF, Obritsch W, Donoso LA. Identification of a potent new pathogenic site in human retinal S-antigen which induces experimental autoimmune uveoretinitis in LEW rats. Cell Immunol 1990;128:209-19.
38. de Smet MD, Bitar G, Wiggert B, Nussenblatt RB. Human S-antigen determinant recognition in patients with uveitis. Invest Ophthalmol Vis Sci 2001;42:3233-8.
39. Davey MP, Rosenbaum JT. The human leukocyte antigen complex and chronic ocular inflammatory disorders. Am J Ophthalmol 2000;129: 235-43.
40. Huhtinen M, Karma A. HLA-B27 typing in the categorization of uveitis in a HLA-B27 rich population. Br J Ophthalmol 2000;84:413-6.
41. Chajek-Shaul T, Pisanty S, Knobler H, Matzner Y, Glick M, Ron N, et al. HLA-B51 may serve as an immunogenic marker for a subgroup of patients with Behcet's syndrome. Am J Med 1984;83:666-72.
42. Kilmartin DJ, Finch A, Acheson RW. Primary association of HLA-B51 with Behcet's disease in Ireland. Br J Ophthalmol 1997;81:649-53.
43. Graham EM, Standord MR, Whitcup SM. Retinal vasculitis. In: Pepose JS, Holland GN, Wilhelmus KR, eds. Ocular infection and immunology. St. Louis: Mosby, 1996, pp. 538-59.
44. Kurhan-Yavuz S, Direskeneli H, Bozkurt N, Ozyazgan Y, Bavbek T, Kazokoglu H, et al. Anti-MHC autoimmunity in Behcet's disease: T cell responses to an HLA-B-derived peptide cross reactive with retinal-S antigen in patients with uveitis. Clin Exp Immunol 2000;120:162-6.
45. Ishihara M, Ishida T, Mizuki N, Inoko H, Ando H, Ohno S. Clinical features of sarcoidosis in relation to HLA distribution and HLA-DRB3 genotyping by PCR-RFLP. Br J Ophthalmol 1995;79:322-5.
46. Goldberg AC, Yamamoto JH, Chiarella JM, Marin ML, Sibinelli M, Neufeld R, et al. HLA-DRB1*0405 is the predominant allele in Brazilian patients with Vogt-Koyanagi-Harada disease. Human Immunol 1998; 59:183-8.
47. Kobayashi H, Kokubo T, Takahashi M, Sato K, Miyokawa N, Kimura S, et al. Tyrosinase epitope recognized by an HLA-DR–restricted T-cell line from a Vogt-Koyanagi-Harada disease patient. Immunogenetics 1998;47:398-403.
48. Yamaki K, Kondo I, Nakamura H, Miyano M, Konno S, Sakuragi S. Ocular and extraocular inflammation induced by immunization of tyrosinase related protein1 and 2 in lewis rats. Exp Eye Res 2000;71: 361-9.
49. Charteris DG, Barton K, McCartney AC, Lightman SL. CD4+ lymphocyte involvement in ocular Behcet's disease. Autoimmunity 1992;12: 201-06.
50. Chan CC, Wetzig RP, Palestine AG, Kuwabara T, Nusenblatt RB. Immunohistopathology of ocular sarcoidosis. Report of a case and discussion of immunopathogenesis. Arch Ophthalmol 1987;105:1398-1402.
51. Doekes G, Luyendijk L, Gerritsen MJ, Kijlstra A. Anti-retinal S-antigen antibodies in human sera: a comparison of reactivity in ELISA with human or bovine S-antigen. Int Ophthalmol 1992;16:147-52.
52. Hoekzema R, Hwan SB, Rothova A, van Haren MA, Donoso LA, Kijlstra A. Serum antibody response to human and bovine IRBP in uveitis. Curr Eye Res 1990;9:1177-83.
53. Ongkosuwito JV, Feron EJ, van Doornik CE, Van der Lelij A, Hoyng CB, La Heij EC, et al. Analysis of immuno-regulatory cytokines in ocular fluid samples from patients with uveitis. Invest Ophthalmol Vis Sci 1998;39:2659-65.
54. Klok AM, Luyendijk L, Zaal MJ, Rothova A, Kijlstra A. Soluble ICAM-1 serum levels in patients with intermediate uveitis. Br J Ophthalmol 1999;83:847-51.
55. Calder VL, Shaer B, Muhaya M, Mclauchlan M, Pearson RV, Jolly G, et al. Increased CD4+ expression and decreased IL-10 in the anterior chamber in idiopathic uveitis. Invest Ophthalmol Vis Sci 1999;2019-24.
56. Kitaichi N, Kotake S, Sasamoto Y, Namba K, Matsuda A, Ogasawara K, et al. Prominent increase of macrophage migration inhibitory factor in the sera of patients with uveitis. Invest Ophthalmol Vis Sci 1999;40: 247-50.
57. Sakaguchi M, Sugita S, Sagawa K, Itoh K, Mochizuki M. Cytokine production by T cells infiltrating in the eye of uveitic patients. Jpn J Ophthalmol 1998;42:262-8.
58. de Smet MD, Dayan M, Nussenblatt RB. A novel method for the determination of T-cell proliferative responses in patients with uveitis. Ocul immunol Inflam 1998;6:173-8.
59. Esin S, Gul A, Hodara V, Jeddi-Tehrani M, Dilsen N, Konice M, et al. Peripheral blood T cell expansions in patients with Behcet's disease. Clin Exp Immunol 1997;107:520-27.
60. de Smet MD, Dayan M. Prospective determination of T cell responses to S-antigen in Behcet's disease patients and controls. Invest Ophthalmol Vis Sci 2000;41:3480-4.
61. Whitcup SM, Salvo EC Jr, Nussenblatt RB. Combined cyclosporine and corticosteroid therapy for sight-threatening uveitis in Behcet's disease. Am J Ophthalmol 1994;118:39
62. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol 2000;130:492-513.
63. Yazici H, Pazarli H, Barnes CG, Tuzun Y, Ozyazgan Y, Silman A, et al.

A controlled trial of azathioprine in Behcet's syndrome. N Engl J Med 1990;322:281
64. Benitez-Del-Castillo JM, Garcia-Sanchez J, Iradier T, Banares A. Sulfadiazine in the prevention of anterior uveitis associated with ankylosing spondylitis. Eye 2000;14:340-3.
65. Reiff A, Takei S, Sadeghi S, Stout A, Shaham B, Bernstein B, et al. Etanecept therapy in children with treatment-resistant uveitis. Arthritis Rheum 2001;45:1411-5.
66. Kotter I, Eckstein AK, Stubiger N, Zierhut M. Treatment of ocular symptoms of Behcet's disease with interferon alpha 2a: a pilot study. Br J Ophthalmol 1998;82:488-94.
67. Dick AD, Meyer P, James T, Forrester JV, Hale G, Waldmann H, et al. Campath-1H therapy in refractory ocular inflammatory disease. Br J Ophthalmol 2000;84:107-9.
68. Nussenblatt RB, Fortin E, Schiffman R, Rizzo L, Smith J, Van Veldhuisen P, et al. Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb; phase I/II clinical trial. Proc Natl Acad Sci U S A 1999;96:7462-6.
69. Thurau SR, Wildner G, Reiter C, Riethmuller G, Lund OE. Treatment of endogenous uveitis with anti-CD4 monoclonal antibody: first report. Ger J Ophthalmol 1994;3:409-13.
70. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. Am J Ophthalmol 1999;127:545-9.
71. Jaffe GJ, Ben-Nun J, Guo H, Dunn JP, Ashton P. Fluocinolone acetonide sustained drug delivery devise to treat severe uveitis. Ophthalmology 2000;107:2024-33.
72. Blank M, George J, Barak V, Tincani A, Koike T, Shoenfeld Y. Oral tolerance to low dose beta 2 glycoprotein I: immunomodulation of experimental antiphospholipid syndrome. J Immunol 1998;161:5303-12.
73. Weiner HL, Mackin GA, Matsui M, Orav EJ, Khoury SJ, Dawson DM, et al. Double-blind pilot trial or oral tolerization with myelin antigens in multiple sclerosis. Science 1993;259:1321
74. Trentham DE, Dynesius-Trentham RA, Orav EJ, Combitchi D, Lorenzo C, Sewell KL, et al. Effects of oral administration of type II collagen on rheumatoid arthritis. Science 1993;261:1727
75. Nussenblatt RB, Gery I, Weiner HL, Ferris FL, Shiloach J, Remaley N, et al. Treatment of uveitis by oral administration of retinal antigens: results of a phase I/II randomized masked trial. Am J Ophthalmol 1997;123:583-92.
76. Thurau SR, Diedrichs-Mohring M, Fricke H, Burchardi C, Wildner G. Oral tolerance with an HLA-peptide mimicking retinal autoantigen as a treatment of autoimmune uveitis. Immunol Lett 1999;68:205-12.