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REVIEW

Advances in the diagnosis and immunotherapy for ocular inflammatory disease

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Abstract Significant advances in the diagnosis and therapy for uveitis have been made to improve the quality of care for patients with ocular inflammatory diseases. While traditional ophthalmic examination techniques, fluorescein angiography, and optical coherence tomography continue to play a major role in the evaluation of patients with uveitis, the advent of spectral domain optical coherence tomography and fundus autofluorescence into clinical practice provides additional information about disease processes. Polymerase chain reaction and cytokine diagnostics have also continued to play a greater role in the evaluation of patients with inflammatory diseases. The biologic agents, a group of medications that targets cytokines and other soluble mediators of inflammation, have demonstrated promise in targeted immunotherapy for specific uveitic entities. Their ophthalmic indications have continued to expand, improving the therapeutic armentarium of uveitis specialists.

Keywords Uveitis · Biologics · Immunosuppression · Polymerase chain reaction · Cytokine

Introduction

Uveitis, which is derived from *uva* (Latin for grape) is defined as an inflammation of the uveal tract or middle coat of the eye (iris, ciliary body, and choroid). In clinical practice, the uveitis specialist is confronted with diagnostic and treatment dilemmas involving not only inflammation of the uvea but also inflammatory syndromes involving other ocular, orbital, and periorbital structures. Some of the more common nonuveal tract inflammatory processes include inflammations of the orbit, (i.e., orbital pseudotumor), sclera (scleritis), and retinal vascular inflammation (retinal vasculitis).

Determining the etiology of a uveitis syndrome may be a difficult task, but it is especially important in ophthalmic conditions associated with a systemic disease. For example, scleritis may be associated with a number of systemic conditions including rheumatoid arthritis, systemic lupus erythematosus, gout, rheumatoid arthritis, or sarcoidosis. Scleritis may also be associated with infectious diseases such as tuberculosis and syphilis. Panuveitis may be associated with sarcoidosis, Vogt–Koyanagi–Harada's disease (VKH), Behçet's disease, or may also represent a masquerade syndrome such as endophthalmitis from systemic bacteremia [1].

After determining the diagnosis of a particular inflammatory condition and excluding an infectious process, consideration of an immunosuppressive regimen is the next important decision faced by the ocular inflammatory specialist. While corticosteroids remain a mainstay of therapy for acute, noninfectious uveitis, the multiple side effects associated with long-term corticosteroid use warrant the consideration of other therapeutic options. The use of immunosuppressive medications such as the antimetabolites (methotrexate, mycophenolate mofetil, azathioprine), T cell calcineurin inhibitors (cyclosporine, tacrolimus), and alkylating agents (cyclophosphamide, chlorambucil) have demonstrated efficacy in the treatment of uveitis with long-term drug-free remissions in some cases [2, 3]. However, each medication has its unique side effect profile requiring laboratory testing, and stringent long-term follow-up is

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required to ensure that the adverse systemic effects associated with the medication do not outweigh the visual benefits. A newer class of medications, the biologic agents, comprises a number of medications directed against specific cytokines, cytokine receptors, cellular adhesion molecules, and other soluble mediators of inflammation. The biologic agents have shown promise in immunotherapy for ocular inflammatory disease, and ophthalmic indications for their use will likely continue to expand [4, 5].

Animal models of uveitis including experimental autoimmune uveitis (EAU) in rodents have been particularly instructive in unraveling the pathogenic mechanisms of uveitis and have been useful for testing novel immunomodulatory agents. While a complete discussion of the many contributions derived from EAU and other animal models of uveitis is beyond the scope of this review, some of the therapies discussed in this review will reference the EAU literature [6, 7].

Inflammatory mechanisms have also been implicated in other ophthalmic conditions including diabetic retinopathy and age-related macular degeneration (ARMD) [8, 9]. Whether an inflammatory insult is the inciting agent or a result of another pathogenic mechanism for these conditions is not clear. In ARMD, inflammatory mechanisms implicated include elements of the complement cascade, particularly complement factor H [10, 11] and cellular components including macrophages and multinucleated giant cells, which have been identified in histopathologic specimens of patients with ARMD [12, 13]. In diabetic retinopathy, the role of a number of inflammatory cytokines, chemokines, and adhesion molecules involved in leukocyte trafficking has been studied and may contribute to low-grade subclinical inflammation [9]. Research efforts continue to be performed in these areas, and immunotherapy may play a role in these conditions in the future. The pathways underlying uveitis and related ocular inflammatory syndromes have been characterized extensively, and advances in the clinical diagnosis of and immunotherapy of these conditions will be discussed in this review.

Specifically, this review focuses on recent advances in the clinical diagnosis and treatment of anterior, intermediate, posterior, and panuveitis. The diagnostic modalities available to clinicians for the evaluation of uveitis have continued to improve over the last decade with increasingly sophisticated laboratory testing (e.g., polymerase chain reaction [PCR], cytokine evaluation, flow cytometry) and ophthalmic imaging techniques (e.g., fundus autofluorescence [FAF], three-dimensional spectral domain optical coherence tomography [OCT]). Significant advances in immunotherapy have also been made, particularly with the increasing use of biologic agents. A number of local therapies including local sustained-release corticosteroid delivery systems (e.g., fluocinolone acetonide implant, intravitreal dexamethasone delivery system) have also been developed and will be discussed in this review.

Classification of uveitis

The anatomic classification of uveitis serves as a useful starting point to guide the differential diagnosis and therapy of an ocular inflammatory condition. The Standardization of Uveitis Nomenclature Working Group convened to establish a classification and grading scheme for uveitis and determined that the anatomic classification of uveitis be used. The scheme was designed not only to provide uniformity in the classification of disease processes but also to permit meta-analyses and to standardize the evaluation of outcomes of patients treated with novel immunotherapies [14].

Anterior uveitis refers to inflammation involving the iris and ciliary body, and terms such as iritis, iridocyclitis, and cyclitis are no longer used. While anterior uveitis is often idiopathic, systemic conditions that may be associated with anterior uveitis include sarcoidosis, tuberculosis, syphilis, and human leukocyte antigen (HLA)-B27-related diseases (i.e., ankylosing spondylitis, Reiter syndrome, Crohn's disease). Anterior uveitis may also be toxic, medication related, as seen with metipranolol therapy [15].

Intermediate uveitis refers to the subset of uveitis in which inflammation is primarily observed in the vitreous cavity. Pars planitis, which had previously been used by some uveitis specialists as being synonymous with intermediate uveitis, is a designated subset of intermediate uveitis (i.e., intermediate uveitis of the pars plana subtype). While intermediate uveitis may be idiopathic, it may also reflect a systemic infection or inflammatory process such as Lyme disease, syphilis, or tuberculosis. Localized ocular infectious causes including *Toxoplasmosis gondii* and *Toxocara canis* are often included in the differential diagnosis of intermediate uveitis. However, these infectious etiologies of intermediate uveitis are more commonly implicated in cases of retinochoroiditis with an associated vitritis. Multiple sclerosis may also be associated with intermediate uveitis, and a magnetic resonance imaging scan and neurologic evaluation may be warranted in patients with a suggestive clinical history.

Posterior uveitis refers to inflammation of the choroid and retina and may result from localized ocular inflammation or from a systemic condition. For example, birdshot retinochoroidopathy and serpiginous choroidopathy only affect ophthalmic structures. Posterior uveitic syndromes with systemic associations include VKH, sarcoidosis, Behçet's disease, tuberculosis choroidopathy, and syphilis. Sympathetic ophthalmia may present with ophthalmic

manifestations alone or with both ophthalmic and systemic findings.

Panuveitis involves inflammation of the anterior, intermediate, and posterior uveal structures, and the differential diagnosis is similar to that of posterior uveitis. Herpetic viral retinitides may also present as panuveitis or posterior uveitis in both immunosuppressed and immunocompetent individuals, and diagnostic strategies are continuing to be developed for the diagnosis of these infectious viral conditions.

Another group of diseases, termed masquerade syndromes, may present with characteristics of ocular inflammatory disease such as vitritis or posterior segment inflammation but are caused by neoplastic or infectious processes. For example, primary intraocular lymphoma (PIOL) may masquerade as an intermediate or posterior uveitis. Recognition of this central nervous system neoplasm in the differential diagnosis of intermediate uveitis is critical to avoid potentially missing a life-threatening diagnosis. Endophthalmitis may present with indolent inflammation (e.g., *Propiobacterium acnes*) or severe intraocular inflammation (e.g., *B. cereus* endophthalmitis), and therapy may include antibiotics and surgical therapy in some situations.

Diagnostic evaluation for the uveitis patient, which may include ancillary ophthalmic testing (e.g., fluorescein angiography [FA], OCT), analysis of serum, aqueous or vitreous specimens, or radiographic imaging, is currently recommended for patients who present with intermediate, posterior, or panuveitis. Patients with anterior uveitis who demonstrate recurrent disease, uveitis recalcitrant to topical corticosteroids, or bilateral anterior uveitis require additional diagnostic workup for an underlying etiology. Each patient's workup will vary depending on the history and exam features of their disease, anatomic location of the inflammatory process, and risk factors for a particular uveitic syndrome.

History and ophthalmic examination

The clinical ophthalmologic evaluation includes a careful history, ophthalmic exam, and review of systems with attention to other potential systemic inflammatory symptoms (e.g., back pain in ankylosing spondylitis, fevers, productive cough, or night sweats suggestive of pulmonary tuberculosis). Past medical history including history of autoimmune diseases, cancer, and systemic immunodeficiency, travel history to areas that may be endemic for certain uveitic syndromes (e.g., West Nile chorioretinitis, onchocerciasis in sub-Saharan Africa), and family history of ocular inflammatory disease (e.g., juvenile systemic granulomatosis) should be elicited. Medications, medication allergies, and social history including use of illicit drugs should also be documented, as these may influence the therapeutic options available to a patient.

The history taking should be directed and relate to the major ophthalmic complaint (e.g., visual acuity loss, peripheral visual field loss, photophobia, floaters). The rapidity of the symptom onset should be ascertained, as some uveitic syndromes such as HLA-B27-associated anterior uveitis are associated with sudden onset of symptoms, while other syndromes may be more indolent in nature. The duration of the uveitis is described as limited if it is less than 3 months or persistent for conditions lasting greater than 3 months. The course of the uveitic syndrome may be characterized as acute, if the condition is a sudden onset and with a limited duration, recurrent if a relapse occurs greater than 3 months after discontinuing therapy, and chronic, if a relapse occurs less than 3 months after discontinuing therapy [14]. These descriptors have relevance to the differential diagnosis of an ophthalmic condition, as well as tailoring therapies for the inflammatory process. In addition, history of prior therapies, a patient's response to therapy, and past ophthalmic history should be thoroughly investigated.

The ophthalmic exam should be thorough, but emphasis should be placed on anatomic structures likely to be implicated based on the patient's symptoms (e.g., photophobia associated with anterior chamber inflammation in anterior uveitis; floaters associated with vitritis in intermediate uveitis). Key elements of the ophthalmic exam include visual acuity, pupillary examination, visual field testing, ocular motility testing, slit lamp biomicroscopic exam, and dilated funduscopic exam. Visual acuity loss may be due to a variety of etiologies including anterior segment disease involving the cornea (e.g., corneal edema) or lens (e.g., cataract), as well as vitreous debris or cystoid macular edema (CME), a complication seen in a number of uveitic entities. Pupils should be assessed for a relative afferent pupillary defect, which may implicate widespread retinal dysfunction or an optic nerve process. Slit lamp examination may reveal perilimbal conjunctival inflammation (ciliary flush), which is suggestive of ciliary body inflammation, granulomatous or nongranulomatous keratic precipitates on the corneal endothelium, and anterior chamber cell and flare resulting from anterior uveitis. Examination of the iris may demonstrate granulomatous nodules on the surface of the iris suggestive of sarcoidosis or posterior synechiae, adhesions forming from the iris to the lens. Patients with uveitis may also develop cataracts from corticosteroid therapy or from long-standing inflammation. The anterior vitreous should also be assessed for vitreous inflammation and the presence of pigment. Dilated funduscopic examination may reveal optic disc edema, macular edema, retinal vascular sheathing from white blood cells

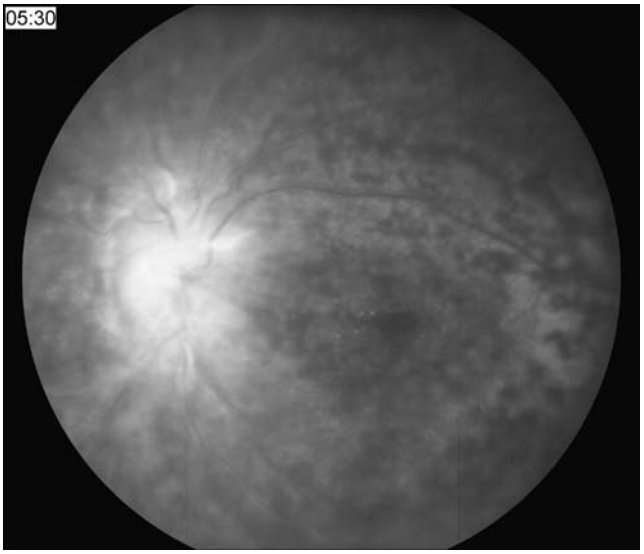

Fig. 1 Fluorescein angiogram in late venous phase shows hyperfluorescence of optic nerve due to inflammation

enveloping retinal vessels, or retinal or choroidal lesions (e.g., birdshot retinochoroidopathy and serpiginous choroidopathy). A thorough ophthalmic exam is essential for accurate anatomic classification of the disease process, identification of the secondary complications of ocular inflammation (e.g., CME), construction of a broad differential diagnosis, and directed ancillary clinical and laboratory testing.

Ancillary testing

Ancillary testing routinely performed in the clinic for the evaluation of uveitis now includes FA and OCT in cases of intermediate, posterior, and panuveitis. FAF has been increasingly utilized in the evaluation of inflammatory processes involving the retina, retinal pigment epithelium (RPE), and choroid. Three-dimensional OCT has also been used in the evaluation of posterior segment processes, and its indications in ocular inflammatory disease will likely continue to increase. B-scan ultrasound continues to play a role in the evaluation of vitreous disorders and retinal and choroidal processes. In addition, laboratory testing including PCR-based testing, cytokine fluid analysis, and flow cytometry may contribute valuable information in the diagnostic workup of a uveitis patient.

Fluorescein angiography

FA remains a mainstay in the clinical evaluation of uveitis for the evaluation of optic disc leakage, macular edema, and retinal vascular leakage. Sodium fluorescein dye is given via intravenous injection and is visualized as hyper- or hypofluorescence within choroidal and retinal structures with an absorption wavelength of 460–495 nm and emission wavelength of 520–530 nm. Hyperfluorescence of the optic nerve may represent optic disc edema either as a primary process (i.e., optic neuritis) or as a secondary sequela of intraocular inflammation (Fig. 1). CME is visualized on FA as a petalloid accumulation of fluorescein dye extravasates into the outer plexiform layer of the retina (Fig. 2). Leakage of fluorescein in a perivascular location may also be a primary process (i.e., retinal vasculitis) or be secondary to intraocular inflammation (e.g., periphlebitis secondary to sarcoid-associated panuveitis). Decreased fluorescence or hypofluorescence may occur due to the blockage of underlying choroidal fluorescence due to retinal pigment epithelial alteration or scarring or may result from retinal ischemia, observed in some cases of retinal vasculitis. For example, in lupus vasculitis, decreased fluorescence is seen due to small-vessel capillary dropout, which may predispose patients to retinal neovascularization and visual loss from foveal ischemia (Fig. 3). The advent of digital FA has provided a method of rapid transfer of data, so that consultation with another physician from a remote location regarding a complex patient is possible.

Fundus autofluorescence

FAF has also been valuable in the evaluation of uveitic syndromes, and its use will likely increase with standardization of FAF photography and improved understanding of this diagnostic modality [16]. FAF relies on the property of autofluorescence, an intrinsic property of some cellular structures due to intracellular photoreactive components

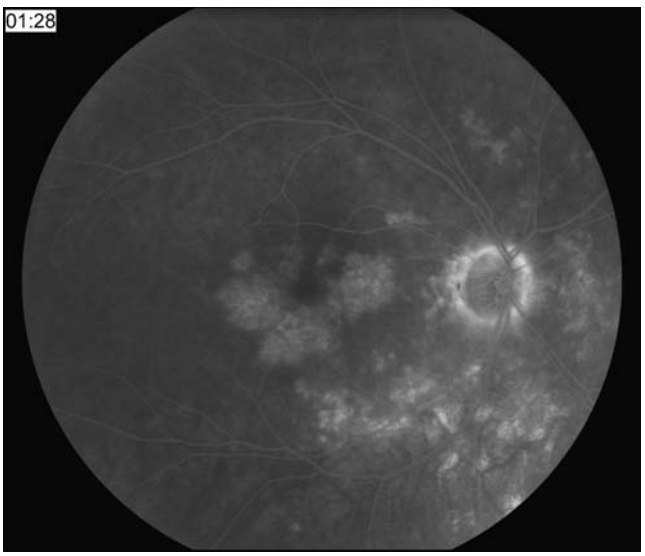

Fig. 2 In this patient, with birdshot retinochoroidopathy, fluorescein dye extravasates into cystoid spaces inferior, nasal, and temporal to the fovea due to incompetence of perifoveal vessels. Hyperfluorescent regions surrounding the optic nerve are due to areas of retinal pigment epithelial dropout

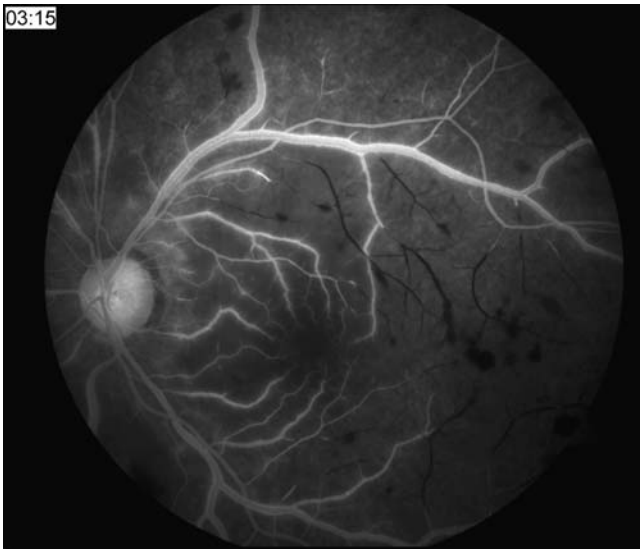

Fig. 3 In lupus vasculitis, numerous capillary vessel dropouts are observed on angiography, resulting in retinal nonperfusion during an episode of active inflammation

[17]. When excited at a particular wavelength, the autofluorescent signal may be detected with the correct barrier filter. The FAF signal from posterior segment structures is derived primarily from lipofuscin, which normally accumulates in aged RPE [18]. A number of filter sets (excitation and barrier filters) have been described for use in the clinical setting. Spaide described the clinical use of an excitation wavelength of 585 nm and barrier filter of 690 nm [19]. Indocyanine green filters (excitation wavelength 790 nm, barrier filter 810 nm) have also been used. In pathologic conditions such as ARMD and central serous chorioretinopathy, distinct FAF patterns have been identified and, in some cases, may be correlated with ongoing and possibly future injury [20, 21]. FAF abnormalities have been reported in a number of ocular inflammatory conditions including acute posterior multifocal pigment placoid epitheliopathy [22], acute syphilitic chorioretinopathy [23], and acute zonal occult outer retinopathy [24]. The FAF signal has also been evaluated in a number of degenerative conditions including retinitis pigmentosa [25], Stargardt's disease (fundus flavimaculatus) [26], Best vitelliform macular dystrophy [27], and pseudoxanthoma elasticum [28]. In uveitic entities involving the retina, RPE, and choroid, we have observed abnormalities of the FAF signal (unpublished data), and this technique will likely continue to provide valuable information about structural changes found in posterior uveitis (Fig. 4).

Optical coherence tomography

The use of OCT in the clinical evaluation of patients with ophthalmic disease was first reported in 1991 by Huang et al. [29]. This noninvasive imaging modality initially demonstrated 10-μm resolution and the ability to visualize cross-sectional anatomy of anterior segment and posterior segment tissues. OCT relies on optical reflectivity to image various planes of retinal tissue similar to ultrasound technology, and its use in the evaluation of uveitis has been previously reported [30]. Macular edema, a secondary complication of a number of uveitic syndromes, is responsible for a significant proportion of uveitis patients with visual loss. Several different patterns of macular edema have been identified in patients with uveitis, including serous neurosensory retinal detachment, diffuse macular edema, and CME [31, 32]. In one study, distance visual acuity was negatively correlated with retinal thick-

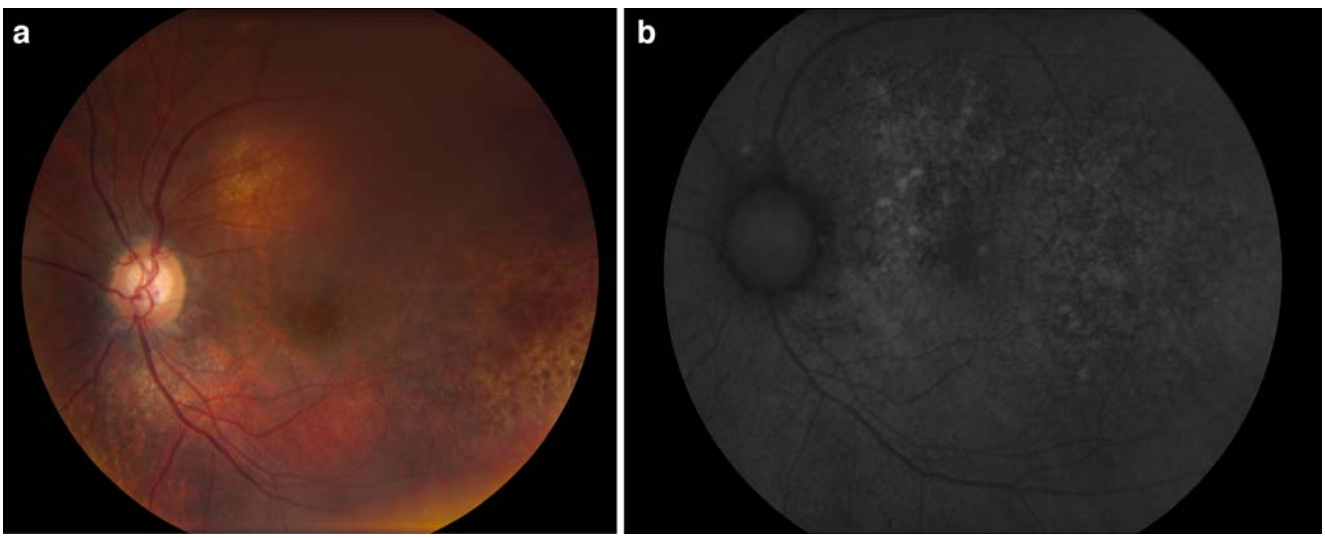

Fig. 4 **a** Fundus photo of patient with VKH showing nummular areas of RPE hyperpigmentation and RPE loss. **b** Corresponding FAF photo of VKH patient shows mottled areas of hyperfluorescent (*bright*) signal amid areas of reticulated hypofluorescent (*dark*) signal, demonstrating widespread RPE abnormalities and accumulation of lipofuscin deposits

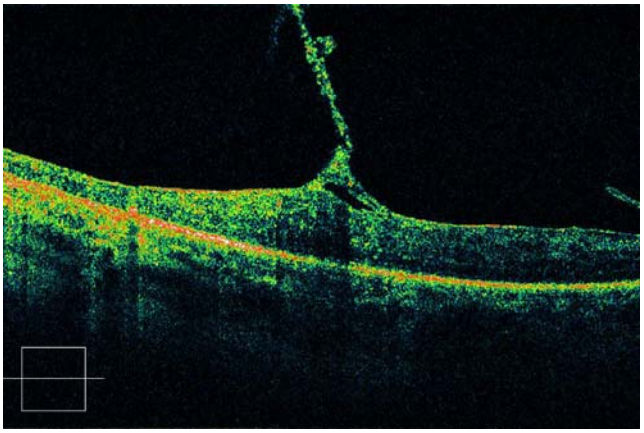

Fig. 5 OCT demonstrates zone of vitreo-macular traction with tenting of the fovea and resultant visual loss

ness, CME, and the presence of a serous retinal detachment [31]. In another study, retinal thickness as measured by OCT appeared to be better correlated to reading (near) acuity and reading speed than distance visual acuity [33]. Quantitative OCT measures of retinal thickness and qualitative interpretation of OCT images have been useful in following the response of patients to immunotherapy. In a study of 50 patients with uveitis, Sivaprasad et al. observed that patients with diffuse macular edema, serous retinal detachments, and outer retinal edema appeared to respond the best to anti-inflammatory medication; cysts of the inner retina did not fare as well and were more resistant to treatment [34]. Complications of uveitis, including vitreomacular traction, epiretinal membrane formation, and posterior vitreous abnormalities, are readily visualized and monitored using OCT (Fig. 5).

The introduction of spectral domain/Fourier transform three-dimensional OCT into clinical practice has improved the ability to resolve retinal microstructures including inner segment and outer segment portions of photoreceptors. Three-dimensional OCT with spectral/Fourier domain technology has improved axial resolution from 10-μm to 2–3-μm resolution. Its faster acquisition time when compared to conventional OCT and ability to record three-dimensional images of retina and optic nerve pathology will likely complement the clinical exam in detecting and following ocular inflammatory disease involving posterior segment structures. Utilizing high-speed ultrahigh-resolution three-dimensional OCT, Srinivasan et al. examined 588 eyes of 327 patients with macular pathology including macular holes, ARMD, epiretinal membranes, diabetic retinopathy, and central serous retinopathy. They described improved image quality, coverage of macular area, and anatomic registration with high-definition 3D OCT when compared to standard OCT [35]. High-resolution three-dimensional OCT has been particularly useful in the volumetric analysis of uveitic entities and in visualizing pathology in three-dimensional space. Sophisticated software analysis has also provided a means to visualize topographic features of individual layers including the RPE, internal limiting membrane, and difference maps between the RPE and internal limiting membrane (Fig. 6).

B-Scan ultrasound

B-scan ultrasound is a safe, noninvasive method of visualizing the anatomic status of the vitreous, retina, and choroid. Ultrasound examination has been most useful in cases of uveitis in which the posterior pole cannot be visualized, usually due to media opacity (e.g., diffuse corneal edema, severe cataract, diffuse vitreous hemorrhage, or severe vitreous haze). In cases of VKH and

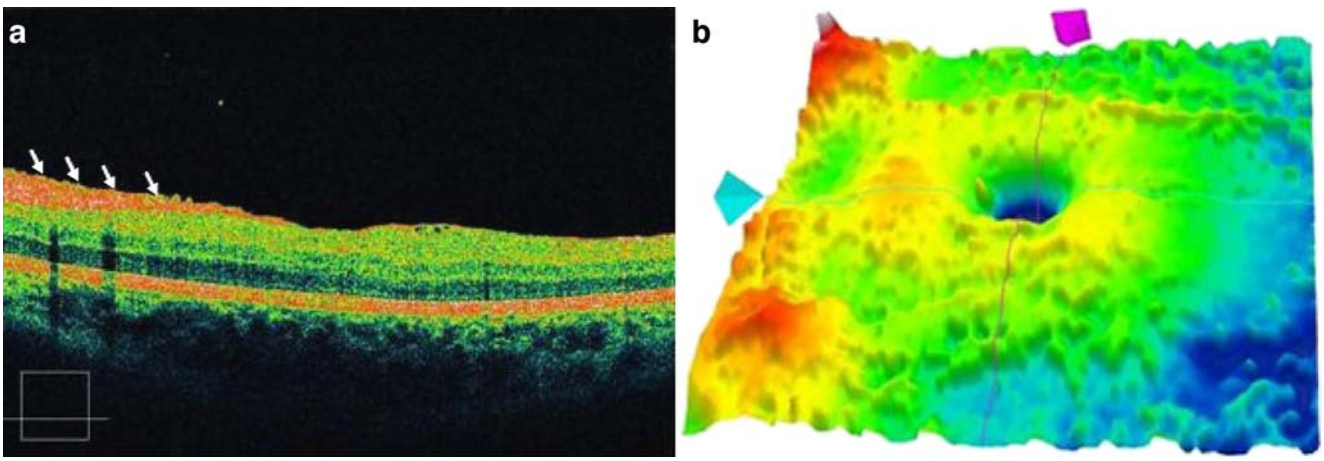

Fig. 6 **a** High-resolution three-dimensional OCT demonstrates the focal epiretinal membrane (*arrows*) leading to mild metamorphopsia. **b** Segmentation of retinal layers on high-resolution 3D OCT allows visualization of the epiretinal membrane in three-dimensional space. The difference in elevation between RPE and the internal limiting membrane pictured here allows improved visualization of the focal epiretinal membrane formation (*red*/*orange color*). The foveal contour is normal (*central blue depression*) with normal visual acuity

posterior scleritis, characteristic findings have also been seen that may be useful to follow during treatment [36, 37]. In VKH for example, ultrasound features include low to medium reflectivity of the choroid, serous retinal detachment, and thickening of the sclera.

Higher-frequency ultrasound in the 40- to 60-MHz range is utilized in ultrasound biomicroscopy (UBM) and may be utilized for the detection of anterior segment pathology with improved visualization of the iris, ciliary body, and pars plana structures. For example, ciliary body effusions and anterior fibrovascular proliferation of the pars plana may be visualized using UBM. UBM has been particularly useful in cases of chronic hypotony due to uveitis and in patients with intermediate uveitis in several reports [38, 39]. In two independent reports, ciliary body abnormalities were observed in approximately 80% of eyes evaluated for ocular hypotony [40, 41]. Uveitis patients with ocular hypotony appeared to derive the greatest benefit from UBM evaluation, and in one report, therapeutic intervention for this condition resulted in the restoration of normal intraocular pressure in 50% of cases [40].

Laboratory studies

The role of laboratory studies in the evaluation of patients with uveitis requires careful consideration because of the significant expenditure on unnecessary laboratory testing, as well as problems with false-positive results including errant diagnosis and unnecessary therapy at times. Serologic and laboratory investigations should be guided by a limited differential diagnosis. If the pretest likelihood of a disease is high, a positive test may serve to confirm clinical suspicions. However, if the pretest likelihood of a disease is extremely low (e.g., systemic lupus erythematosus in a patient with isolated anterior uveitis), the likelihood of a patient having lupus with a positive antinuclear antibody test result still remains very low [42]. The choice of laboratory investigations for anterior, intermediate, posterior, and panuveitis should be tailored according to the diagnostic possibilities, as opposed to a "shotgun" approach to laboratory testing. Patients who have bilateral, granulomatous anterior uveitis from an area endemic for tuberculosis may require PPD testing and a chest X-ray; in other patients with unilateral, acute anterior uveitis responsive to a short course of topical corticosteroid, no evaluation may be necessary.

Polymerase chain reaction-based testing

The emergence of PCR testing of ocular fluid for uveitic syndromes has improved our ability to more accurately diagnose herpetic viral retinitides, toxoplasmosis, toxocariasis, and *Mycobacteria* infections in some cases [43, 44]. The list of etiologies that PCR allows us to identify will likely increase as PCR techniques continue to improve. PCR testing has been valuable in the confirmation of atypical cases of cytomegalovirus (CMV) retinitis [45], as well as in the identification of viral etiologies of progressive outer retinal necrosis and acute retinal necrosis (ARN) [46, 47]. Pathogenic viruses identified in ARN thus far have included varicella–zoster virus (VZV), herpes simplex (HSV)-1, HSV-2, and CMV [46]. It is interesting to note that one child with an atypical case of ARN who was serology negative for HSV was diagnosed with HSV-2 retinitis via PCR of an aqueous humor specimen [48]. Real-time quantitative PCR may also have a role in the monitoring of VZV deoxyribonucleic acid (DNA) levels and clinical response during the treatment of progressive outer retinal necrosis and ARN [49, 50].

Besides its use in the diagnosis of the herpetic viral retinitides, PCR diagnostics have also been useful in the diagnosis of serpiginous-like choroiodopathy [51], retinal vasculitis [52], and retinochoroiditis associated with tuberculosis [53]. The use of nested PCR has also been used clinically for the detection of Mycobacterial DNA with promising results [54, 55].

PCR-based testing has also been performed for *T. gondii* retinochoroiditis [56]. However, in cases in which PCR for Toxoplasmosis DNA is negative, an elevation in the local antibody titer to *T. gondii* relative to serum antibody titer levels may contribute to the diagnosis of ocular toxoplasmosis. In one study, calculation of the Goldmann–Witmer coefficient (GWC) was complementary to PCR for DNA of herpetic viruses and Toxoplasmosis. If PCR was the only modality used for diagnosis, herpetic viruses would have been missed in 34% of cases, and Toxoplasmosis would have been missed in 64% of cases [57]. In another retrospective series comparing the utility of PCR and GWC for the diagnosis of 56 patients with uveitis, viral infections were detected by PCR in 16 of 17 cases (94%), while GWC identified *T. gondii* as the cause of an infectious uveitis in nine of ten cases (90%) [58].

Cytokine fluid analysis

Cytokine testing of patient samples obtained from serum and aqueous and vitreous fluids has contributed to our understanding of the pathogenic mechanisms underlying ocular inflammatory disease [59]. Their clinical utility will likely increase, as disease-specific cytokine profiles are characterized.

The ability to distinguish different ocular inflammatory pathologies from cytokine analysis is exemplified in work by Chan et al., which reported an elevation of interleukin (IL)-10 in the vitreous fluids of patients with PIOL. In vitrectomy specimens from patients with PIOL, IL-10

levels were correlated with clinical activity and the number of malignant cells [60]. In clinical practice, an elevation of the vitreous IL-10 level relative to the IL-6 level has been helpful in the diagnosis of intraocular B cell lymphoma [61]. An IL-10 to IL-6 ratio greater than 1.0 has been more frequently observed in vitritis secondary to intraocular lymphoma than in vitritis from other inflammatory etiologies (IL-10/IL-6 less than 1.0) [62].

A number of cytokine-profiling studies have been performed to examine disease-specific cytokine profiles, and their findings may help to guide future immunotherapy. Ahn et al. compared the aqueous and serum cytokine profiles of Behçet's patients with active uveitis to those who were inactive [63]. Interferon (IFN)-γ and tumor necrosis factor (TNF)-α levels were higher in the aqueous fluids of patients with active Behçet's uveitis when compared to patients without uveitis. In addition, the immunoregulatory cytokine IL-10 was expressed in both the aqueous fluids and serum of patients with quiescent Behçet's uveitis but was not observed in patients with active disease. Their findings suggested that a T-helper 1 cell polarization and proinflammatory state were present in Behçet's uveitis. Several studies have also recently supported the use of infliximab, a TNF-α antagonist, in the treatment of active Behçet's disease-associated uveitis (discussed below).

Studies in VKH patients have demonstrated elevated aqueous levels of IL-6 [64], as well as elevated IFN-γ messenger ribonucleic acid (mRNA) from peripheral blood mononuclear cells [65]. Imai et al. also demonstrated higher IFN-γ and IL-2 levels in cell culture supernatant obtained from VKH patients and a higher proportion of CD4+ T-helper cells, which produced IFN-γ and IL-2. The propensity of VKH patients toward a T-helper 1 cell-type cytokine profile may explain, in part, the efficacy of medications such as daclizumab (directed against IL-2 receptor) for this indication (discussed below).

Besides studies examining specific disease entities, a number of observations have been made on cytokine profiles in various classes of uveitis. Takase et al. examined cytokine profiles in serum and aqueous humor samples in infectious and noninfectious uveitis. IFN-γ and IL-10 levels were higher in both aqueous humor and sera samples of both infectious and noninfectious uveitis. It is interesting to note that IFN-γ was elevated in both aqueous fluids and sera of patients with noninfectious uveitic conditions, possibly indicating a systemic inflammatory process, rather than solely local inflammation, as seen in some cases of isolated infectious uveitis [66]. In a study by Curnow et al., multiplex bead immunoassay technology was used to analyze aqueous humor cytokine profiles in noninfectious uveitis versus controls. In their study, IL-6, IL-8, and IFN-γ were elevated in the aqueous humor of patients with idiopathic uveitis; the immunoregulatory cytokine transforming growth factor-β2 was decreased in idiopathic uveitis [67]. In another study comparing multiplex cytokine detection versus enzyme-linked immunosorbent assay for uveitis patients, aqueous humor IFN-γ was elevated in both anterior uveitis and panuveitis patients when compared to controls. IL-10 was notably elevated in patients treated with corticosteroid, implicating glucocorticoid-mediated upregulation of IL-10 as a possible mechanism for its immunosuppressive effect [68].

Advances in immunotherapy

Corticosteroids remain a mainstay for the treatment of active, noninfectious uveitis. However, the myriad of side effects (i.e., hypertension, osteoporosis, hyperglycemia, and growth retardation in children) associated with their long-term use requires the consideration of other corticosteroid-sparing agents including traditional agents such as the antimetabolites, T cell calcineurin inhibitors, and alkylating agents. A newer class of medications, the biologics, targets specific cytokines, cytokine receptors, and other cellular or soluble targets implicated in inflammation, and their use for ophthalmic inflammatory disease continues to increase. Agents in this class include the TNF-α inhibitors (infliximab, adalimumab, etanercept) and the IL-2 receptor daclizumab. Advances in corticosteroid delivery systems have also contributed to the therapeutic options for the ophthalmologist.

The efficacy of the antimetabolites, calcineurin inhibitors, and alkylating agents has been demonstrated for a number of uveitic entities [2, 3]. The antimetabolite class of medications includes mycophenolate mofetil, methotrexate, and azathioprine. Mycophenolate mofetil, the newest medication in this class, inhibits inosine monophosphate dehydrogenase, inhibiting a pathway of guanosine nucleotide synthesis preferentially used by T and B cells. Initially used for the prevention of renal transplant rejection, the efficacy of mycophenolate mofetil for a number of ophthalmic inflammatory diseases has been reported [69]. Some of these ophthalmic diseases include HLA-B27-associated anterior uveitis, juvenile idiopathic arthritis (JIA), scleritis, and several posterior uveitic syndromes (birdshot retinochoroidopathy, VKH, sympathetic ophthalmia) [70, 71]. Azathioprine has also been successfully used for a variety of posterior uveitic syndromes including serpiginous choroidopathy [72, 73], VKH [74], and sympathetic ophthalmia [3]. "Triple therapy" or the combination of cyclosporine, azathioprine, and prednisone has also been valuable in the treatment VKH [75], sympathetic ophthalmia [76], and serpiginous choroidopathy [77]. Methotrexate has demonstrated efficacy for the treatment

of sarcoidosis-associated uveitis, intermediate uveitis, rheumatoid arthritis, and JIA [78, 79]. Primary intraocular lymphoma has also been treated with intravenous methotrexate previously [80]. Each medication requires monitoring of symptoms and laboratory tests because of their associated side effects. Azathioprine may be acutely associated with cytopenias and gastrointestinal disturbances. Mycophenolate may also be associated with gastrointestinal disturbances, but myalgias, fatigue, and headache may also be experienced by patients on this medication. Nonmelanoma skin cancer, leukopenia, and opportunistic infections have also been associated with mycophenolate mofetil use; however, these complications have frequently been observed in heavily immunosuppressed individuals. Side effects of methotrexate include leukopenias, hepatotoxicity, and impairment of renal function. In addition, approximately 1–5% of patients experience an acute pneumonitis due to a drug hypersensitivity reaction [1].

The T cell calcineurin inhibitors cyclosporine [81, 82] and tacrolimus [83] have also been used as immunotherapy for noninfectious, endogenous uveitis. Cyclosporine appears to interfere with T cell activation and recruitment, but the precise mechanism is debatable. Following binding to its immunophilin, cyclosporine is transported to the nucleus where it interferes with mRNA and protein synthesis. Cyclosporine also binds to proteins that bind to an IL-2 enhancer to prevent transcriptional activation of the IL-2 gene [1]. The efficacy of cyclosporine was first demonstrated in animal models of uveitis [84, 85] and, subsequently, in several prospective clinical trials for uveitis [81, 86]. The successful use of cyclosporine for the treatment of uveitis has been reported in a number of posterior uveitic entities including Behçet's disease, sympathetic ophthalmia, serpiginous choroidopathy, birdshot retinochoroidopathy, intermediate uveitis, and pediatric uveitis [1]. Tacrolimus (FK506) binds to its specific immunophilin (FK506-binding protein) and also suppresses the transcription of IL-2 mRNA. Its efficacy has been demonstrated in Behçet's disease, intermediate uveitis, sarcoidosis-associated uveitis, and uveitis refractory to cyclosporine in one case report [87, 88]. Hypertension and renal toxicity are the most common adverse effects that require vigilant monitoring in patients treated with cyclosporine. Alteration in renal function was seen more often when cyclosporine was used at a much higher dose (10 mg kg^{-1} day^{-1}) than the current dose range used for uveitis patients currently (2–5 mg kg^{-1} day^{-1}). Tacrolimus has been associated with nephrotoxicity, tremors, gastrointestinal symptoms, and hyperglycemia [1].

The alkylating agents, cyclophosphamide and chlorambucil, are the least commonly used immunomodulatory agents for uveitis but may be required in cases of severe, bilateral refractory uveitis not amenable to other therapies when visual acuity is salvageable [89, 90]. The efficacy of cyclophosphamide for Wegener's granulomatosis-associated ocular and orbital inflammatory disease has been reported previously [91, 92]. In addition, cyclophosphamide has been used in the treatment of serpiginous choroidopathy and Behçet's disease [93, 94]. Chlorambucil has been used for the treatment of sympathetic ophthalmia [95] and Behçet's disease in several reports [96, 97]. A range of side effects associated with alkylating agents has been reported, but leukopenia and serious opportunistic infections requiring hospitalization and intravenous antibiotics have been reported. Secondary malignancy including bladder cancer in patients who have had hemorrhagic cystitis has been observed with cyclophosphamide use. Other complications of cyclophosphamide include interstitial pulmonary fibrosis and testicular atrophy. Sterility may also be seen in patients on either cyclophosphamide or chlorambucil, and cryopreservation should be considered in any patient considering alkylating agent therapy [1].

Biologic therapy for ocular inflammatory disease

A newer class of medications, the biologics, targets specific cytokines, cytokine receptors, and soluble mediators of inflammation. The use of biologics may allow the treating physician to eventually tailor the immunotherapy against a specific immune target. This will be especially relevant as the specific immune mechanisms of each disease entity are elucidated. Biologic agents have been used for a number of rheumatologic, dermatologic, hematologic, and neurologic indications. In ophthalmic practice, biologic agent therapy is currently considered an off-label use of Food and Drug Administration (FDA)-approved medications. Without FDA approval and the benefit of large prospective, controlled trial data, caution is recommended when considering the use of these medications. Three groups of biologic medications that have been used for ophthalmic indications include the TNF-α antagonists, IL-2 receptor antagonist daclizumab, and the IL-1 receptor antagonist anakinra.

Tumor necrosis factor-α antagonists

In EAU, uveal infiltration of macrophages and T cells has been observed, resulting in the elaboration of proinflammatory cytokines and subsequent loss of tissue architecture and function. TNF-α has also been detected in the aqueous humor of patients with intraocular inflammation and serves as an attractive target for anti-inflammatory therapy [98]. Three TNF-α antagonists are FDA approved for systemic administration—infliximab, adalimumab, and etanercept.

Infliximab (Remicade)

Infliximab is a mouse-derived chimeric monoclonal antibody directed against soluble and transmembrane TNF-α, preventing the binding of TNF-α with its receptor. Several clinical trials have supported the efficacy of infliximab for a number of rheumatologic diseases including rheumatoid arthritis [99, 100], Crohn's disease [101], anklosing spondylitis [102], and psoriatic arthritis [103]. The successful use of infliximab for uveitis associated with Behçet's disease, JIA-associated uveitis, HLA-B27-associated uveitis, and anklyosing spondylitis has been reported in a number of retrospective case series.

Suhler et al. reported their experience in a phase II, open-label study using infliximab for refractory autoimmune uveitis. Diagnoses of patients enrolled in their series included sarcoidosis, pars planitis, Behçet's disease, and Crohn's disease. Infliximab was given in doses of 3 mg/kg or 5 mg/kg via intravenous infusion at weeks 0, 2, and 6, and clinical efficacy was assessed at week 10. Of the 23 patients treated, 18 (78%) of the subjects met the clinical criteria for success at the week 10 time point (i.e., improved visual acuity, two-step decrease in intraocular inflammation, ability to taper immunosuppression, or decrease in inflammatory signs by OCT or FA). Seven (50%) of 14 patients maintained on infliximab for a full year maintained successful grading. Of concern, however, were a number of adverse events observed including congestive heart failure, lupus-like reaction, pulmonary embolus, and vitreous hemorrhage in two patients. Antinuclear antibodies were also found in 15 of 20 patients who received more than three infusions. Thus, while some patients achieved benefit from the medication, the rate of adverse events was unexpectedly high, and the authors recommended additional long-term studies to assess the safety and efficacy infliximab for ocular inflammatory diseases [104].

Niccoli et al. recently reported their experience with infliximab for Behçet's disease-associated uveitis in a 24-month prospective, open-label, multicenter trial. In their study, 9 of 12 (75%) of patients treated with infliximab demonstrated complete remission with no relapses at 12-month follow-up. At the 24-month follow-up, seven of nine (78%) remained in remission. Visual acuity improved, and the number of ocular attacks was decreased compared to the year prior to infliximab therapy [105]. Abu El-Asrar et al. also reported a smaller prospective trial of six patients treated with infliximab. Follow-up varied from 16 to 36 months, but all six patients achieved remission at 2-month follow-up. Two patients experienced uveitic relapses, which resolved following a subsequent infusion of infliximab, and one patient required more frequent infusions (every 6 weeks) because of a relapse while undergoing infusion at 8-week intervals [106]. Tugal-Tutkun et al. described their experience with infliximab in Behçet's disease-associated uveitis in patients who were resistant to combination therapy with corticosteroids, azathioprine, and cyclosporine. Infliximab infusions (5 mg/kg) given at weeks 0, 2, 6, and 14 resulted in remission during the infusion period (weeks 0–22) in 4 (30.8%) of 13 patients. One patient demonstrated a sustained remission without any attacks of uveitis at 54-week follow-up, and 36 total uveitic attacks were documented. However, the number of attacks occurring during the observation period was less than the number during the period prior to infliximab therapy [107].

The treatment of JIA-associated uveitis with infliximab has been reported in several retrospective case series [108, 109]. Richards et al. described the efficacy of infliximab in five of six JIA patients treated with a drug-free remission observed in three patients. Low-dose immunosuppression was continued in combination with infliximab therapy, supporting the role of infliximab as an adjunctive therapy for this ophthalmic indication [109].

The use of infliximab for pediatric uveitis of other etiologies has also been reported. Successful tapering of immunosuppression was reported in six patients treated with infliximab for refractory uveitis by Rajaraman et al. Diagnoses in their series included idiopathic pars planitis, juvenile rheumatoid arthritis, and retinal vasculitis [110]. Kahn et al. reported their experience with high-dose infliximab (10–20 mg/kg) in a series of 17 pediatric patients with refractory uveitis. All 17 patients demonstrated rapid responses with no observed inflammation. This was achieved in 13 of 17 patients after two infusions and in the other four patients after three infliximab infusions [111].

One prospective, noncomparative case series evaluated infliximab (10 mg/kg) as monotherapy for HLA-B27-associated anterior uveitis. In this report, six of seven patients demonstrated total resolution of inflammation, and all patients experienced an improvement of clinical symptoms and decrease in anterior chamber cells. However, relapses were observed in four patients after 5±6.4 months [112].

Besides its efficacy in intraocular inflammation, infliximab has also been successfully used for the treatment of scleritis and peripheral ulcerative keratitis [113]. Murphy et al. retrospectively reviewed their experience with infliximab for three patients with scleritis, one patient with a combination of peripheral ulcerative keratitis, and three other patients with intraocular inflammation. In their series, infliximab given at a dose of 200 mg at 4- or 8-week intervals resulted in clinical improvement in six patients with five achieving remission and one patient experiencing a significant reduction in immunosuppression [114]. Of the patients described, one patient discontinued treatment because of a hypersensitivity reaction. Several case reports

and case series have described the efficacy of infliximab for peripheral ulcerative keratitis and scleritis due to Wegener's granulomatosis [115], rheumatoid arthritis [116], and relapsing polychondritis [117].

Reported adverse effects associated with infliximab therapy include reactivation of latent tuberculosis, the unmasking of demyelinating disease, congestive heart failure exacerbations, the development of antinuclear antibodies, and the formation of anti-infliximab antibodies [104, 106]. Herpes zoster and optic neuritis have also been rarely reported following infliximab therapy [118, 119]. Reports of hepatosplenic lymphoma in young patients receiving infliximab therapy for inflammatory bowel disease have also been worrisome, given the increasing use of this medication in the pediatric population [120]. The potential long-term risk of lymphoma in patients treated with infliximab is of concern and requires further study. A definite causal relationship between anti-TNF therapy and lymphoma has not been established [121], and reports in the literature differ with respect to whether anti-TNF therapy is associated with a higher incidence of lymphoma [122, 123].

Adalimumab (Humira)

Adalimumab is a humanized, recombinant TNF-α-specific immunoglobulin G1 monoclonal antibody, blocking the interaction of TNF-α with the p55 and p75 cell surface receptors. Adalimumab binds to cell-bound TNF-α and may theoretically be more effective in immunosuppression than etanercept, which is a soluble TNF-α receptor.

The use of adalimumab for uveitis has been reported in both adults and pediatric patients. In one retrospective series examining the efficacy of adalimumab in 14 children with uveitis (nine JIA-associated and five idiopathic), decreased inflammation was observed in 21 of 26 eyes (80.8%) with four eyes (15.4%) remaining stable and only one eye worsening (3.8%). Use of adalimumab allowed a decrease in topical corticosteroid usage in 11 of 14 patients (78.5%) with 4 of 14 (28.5%) completely discontinuing drops. Corticosteroid-sparing medications were also discontinued or decreased in a number of patients in this series [124]. Biester et al. reviewed their experience in the use of adalimumab for pediatric uveitis (17 JIA-associated, one idiopathic uveitis) and observed efficacy in 16 of 18 patients (88%). Of note, adalimumab was effective or mildly effective for arthritis in 13 of 16 patients (81%) [125]. Thus, while the efficacy of adalimumab was comparable to etanercept for arthritis, it appeared to be more effective for the treatment of uveitis than etanercept [125].

Two retrospective case series examining the efficacy of adalimumab for uveitis secondary to Behçet's disease have shown promising results. In a report by Mushtaq et al., three patients with bilateral panuveitis due to Behçet's disease were switched successfully from infliximab to adalimumab during a period of clinical remission. At variable follow-up intervals ranging from 11 to 24 months, the intraocular inflammation in all three patients remained well controlled [126, 127].

Adalimumab is given either as a 20- or 40-mg subcutaneous injection on a weekly or biweekly dosing schedule and may be advantageous versus infliximab, which requires an intravenous infusion. The most commonly reported adverse events associated with adalimumab were injection site reactions, occurring in up to 10% of patients. In one trial of adalimumab for ankylosing spondylitis, adverse events were higher in patients treated with adalimumab versus controls; it is interesting to note that the incidence of infections did not appear to be higher in the adalimumab group. No reports of reactivation of latent tuberculosis, demyelinating disorders, drug-induced lupus, congestive heart failure, or secondary malignancies were observed [128]. In a postmarketing surveillance study of rheumatoid arthritis population, adalimumab also appeared to be safe and well tolerated, without an increase in the incidence of lymphoma greater than that observed in rheumatoid arthritis patients [129]. Adverse events reported in the ophthalmic literature include injection site reactions, HSV keratitis, and elevation of liver enzymes requiring the cessation of adalimumab [125].

Etanercept (Enbrel)

Etanercept is a fusion protein composed of the extracellular ligand-binding portion of TNF receptor p75 and the Fc portion of human IgG1. Etanercept has demonstrated efficacy in joint inflammation associated with rheumatoid arthritis [130], JIA [131], psoriatic arthritis [132], and ankylosing spondylitis [133]. However, its efficacy in the treatment of ocular inflammatory disease has been variable.

Schmeling and Horneff reported the findings from questionnaires completed by pediatric rheumatologists to document the incidence of chronic anterior uveitis and associated complications in 310 JIA patients. From the 229 questionnaires returned (74%), 31 patients (13.5%) with 102 uveitic flares were identified in patients who had a history of uveitis prior to etanercept treatment. Following etanercept treatment, 32 uveitis exacerbations were reported in 19 patients; it is interesting to note that two patients experienced their first episode of uveitis. Arthritis significantly or completely responded in 87% of uveitis patients, and etanercept did not appear to influence the frequency or severity of uveitis episodes [134]. A randomized, masked trial of etanercept for JIA-associated anterior uveitis conducted at the National Eye Institute (NEI) demonstrated no difference between etanercept and placebo. Three of

seven patients randomized to etanercept and two of five patients randomized to placebo were considered ophthalmic successes. However, this pilot study was limited by its small sample size [135]. In one case report of a patient with idiopathic panuveitis who only partially responded to multiple immunosuppressive medications (methotrexate, cyclosporine, corticosteroid), etanercept resulted in complete control of his intraocular inflammation [136].

Galor et al. recently compared the efficacy of etanercept versus infliximab in a retrospective analysis. Fifty-nine percent of patients treated with infliximab demonstrated a greater than or equal to 50% reduction in uveitis recurrences on therapy; conversely, none of the patients on etanercept therapy experienced a similar reduction. Seventeen of 18 (94%) patients on infliximab showed a reduction in intraocular inflammation at their final follow-up, whereas zero of four patients on etanercept experienced a reduction in intraocular inflammation [137].

Another recent report by Foeldvari et al. examined the use of the three TNF-α inhibitors for the treatment of JIA-associated uveitis in a cross-sectional survey of 33 pediatric rheumatology centers. In this report, a total of 47 patients on anti-TNF therapy were identified with a mean age of 12.5 years. Etanercept was used in 34 cases, infliximab in 25 cases, and adalimumab in three cases. In 12 of 34 patients in which etanercept was used, the treatment was inefficacious, and patients were subsequently switched to infliximab therapy. In their report, infliximab was more efficacious than etanercept for the treatment of JIA-associated uveitis. Adalimumab was efficacious in all three patients treated [138].

Etanercept is given via subcutaneous injection at a dose of 25–50 mg per dose, twice per week. Of concern are reports of ocular inflammatory exacerbations (scleritis, uveitis, myositis) associated with etanercept therapy [139]. In one case report, acute exacerbations of ankylosing spondylitis-associated uveitis were temporally associated with etanercept injections [140]. Optic neuritis has also been observed in four patients receiving etanercept injections, with three of four patients requiring discontinuation of therapy [141]. A retrospective cohort study, which reviewed 70 patients on etanercept, found no statistically significant increased risk in the development of new-onset uveitis. However, treatment with etanercept was unable to prevent uveitis onset in two patients in their cohort of patients (2.9%) [142].

Daclizumab (Zenapax)

Daclizumab is a humanized monoclonal recombinant immunoglobulin targeting Tac, a 55-kDa IL-2 receptor subunit expressed by most T, B, and natural killer cells. The IL-2 receptor system is a lymphokine receptor system, which plays a key role in the induction of the immune response. Expression of the Tac subunit is considered a critical step in the activation of all T cells that are contributors to autoimmune disease.

In animal models of uveitis, the presence of high-affinity IL-2 receptors has been demonstrated previously [85]. In uveitis patients, levels of soluble IL-2 receptor in both patient serum [143]and aqueous fluids [144] were elevated versus control subjects.

A number of studies have reported the efficacy of daclizumab for the treatment of noninfectious intermediate and posterior uveitis and panuveitis. A nonrandomized, open-label pilot study showed that the use of intravenous daclizumab therapy in up to 4-week intervals allowed patients to successfully taper other immunosuppressive medications. In addition, daclizumab was effective in preventing the expression of sight-threatening inflammatory disease in eight of ten patients treated over a 12-month period. The various diagnoses treated included sarcoidosis, idiopathic intermediate uveitis, VKH, idiopathic panuveitis, and multifocal choroiditis [145]. A longer-term phase I/II interventional study of intravenous daclizumab and a short-term phase II study using subcutaneous daclizumab also has demonstrated encouraging results. Seven of ten enrolled patients in the long-term intravenous daclizumab study were tapered off their original immunosuppressive medications. It is interesting to note that the use of 6-week intervals of daclizumab infusion resulted in recurrent uveitic disease, whereas 2- to 4-week dosing intervals did not. All five patients in the short-term subcutaneous daclizumab study met endpoints for success by 26 weeks of therapy; four of five patients met endpoints for success within the first 12 weeks [146].

A retrospective review by Papaliodis et al. documented the efficacy of daclizumab for a variety of ocular inflammatory diseases including scleritis, ocular cicatricial pemphigoid, and panuveitis [147]. Visual acuity improvement was reported in 12 of 27 (44%) eyes and in 5 of 14 (36%) patients. Intraocular inflammation improved in 16 of 27 eyes (59%), remained stable in 3 of 27 (11%) eyes, and worsened in 8 of 27 (30%) eyes.

Several other retrospective studies have reported the use of daclizumab for a variety of other ocular inflammatory conditions including birdshot retinochoroidopathy and childhood uveitis of varying etiologies [148, 149]. Gallagher et al. reported decreased ocular inflammation in five pediatric patients following the use of daclizumab. Diagnoses in their cohort included sarcoidosis, panuveitis, keratouveitis, and anterior uveitis. Four of ten eyes improved vision, while five of ten eyes remained stable. One eye demonstrated a deterioration of vision in this series [149].

For the uveitis protocol treatments conducted at the NEI, two induction treatments are typically completed within 14 days. A higher-dose induction treatment of intravenous daclizumab at 4–8 mg/kg is given on day 0 followed by another intravenous dose of 2–4 mg/kg at day 14. Maintenance therapy is then continued at 1–2-mg/kg doses in 4-week intervals.

In several studies of daclizumab for the prevention of renal allograft rejection, no difference in serious infectious complications or cancer has been observed when comparing patients receiving daclizumab or placebo [150, 151]. One patient from the NEI was diagnosed with low-grade renal cell carcinoma after 4 years of monthly intravenous daclizumab therapy. The renal cell carcinoma was surgically removed, but it was not clear whether this event preceded intravenous daclizumab therapy. Following surgical removal of the renal cell carcinoma, the participant was restarted on intravenous daclizumab and converted to subcutaneous daclizumab without any further untoward effects.

Anakinra (Kineret)

IL-1 receptor antagonist (IL-1RA) is a naturally occurring protein that inhibits IL-1 activity, downregulating the proinflammatory functions of IL-1 including chemotaxis, activation of antigen-presenting cells, and the upregulation of cell surface adhesion molecules involved in leukocyte trafficking. IL-1RA binds to IL-1 type I receptor competitively with an affinity comparable to IL-1α and IL-1β. During experimentally induced inflammation, IL-1RA limits IL-1 activity presumably through a negative feedback mechanism. Anakinra is a recombinant, human, nonglycosylated IL-1RA. Anakinra competes with the IL-1 ligand-binding site but does not induce downstream signaling pathways after it binds to its target.

In several rodent models for uveitis, increased IL-1α [152152], IL-1β [152, 153], and IL1-RA [154] have been observed. In one therapeutic trial for murine EAU, mice treated with anakinra demonstrated lower levels of clinical and histological inflammation compared to untreated mice and decreased cellular immune response and inflammatory cytokine expression (i.e., IFN-γ, TNF-α, IL-1α, IL-1β, IL-1RA, and IL-6) [155].

Benezra et al. examined the IL-1RA levels of patients with pars planitis, Behçet's disease, and normal volunteers who were naïve to therapy and following immunosuppressive therapy (i.e., corticosteroid and cyclosporine). Prior to immunosuppressive treatment, no difference was observed in IL-1RA levels between uveitis patients and controls. Following immunosuppression, a statistically significant increase in IL-1RA was observed in uveitis patients compared to their baseline mean IL-1RA levels. This study suggests a possible mechanism involved in the immunomodulatory properties of the medications used and a potential immune target for the treatment of uveitis [156].

The efficacy of anakinra in rheumatoid arthritis patients has been reported by Cohen et al. In their report, patients treated with 1.0–2.0 mg/kg anakinra demonstrated significant improvement by the American College of Rheumatology 20% improvement criteria (i.e., ACR20 response) following 12 weeks of therapy when compared with patients receiving placebo. All patients were also on concomitant methotrexate therapy [157]. A noncomparative, open-label study of anakinra for polyarticular JIA also demonstrated encouraging results with 46 of 82 (58%) of patients experiencing clinical improvement [158]. Injection site reactions were the most commonly observed adverse event, occurring in 70% of patients in this series; however, most injection reactions were mild [158].

Thus far, the use of anakinra for ocular inflammatory disease has been limited to few case reports and small case series. Teoh et al. reported the efficacy of anakinra for ocular inflammation associated with chronic infantile neurological cutaneous articular (CINCA) syndrome. In their report, a 4-year-old patient with CINCA syndrome demonstrated resolution of both posterior uveitis and arthritis with anakinra treatment after failing other immunosuppressive medications (i.e., prednisolone, methotrexate, and etanercept) [159]. In another report by Aróstegui et al., anakinra combined with mycophenolate mofetil was successfully used to treat severe uveitis in a 15-year-old female patient with NOD2 gene-associated pediatric granulomatous arthritis. IL-1β, IL-6, and TNF-α had been elevated in the patient's plasma prior to anakinra therapy compared to controls. Following treatment with anakinra, IL-1β, IL-6, and TNF-α normalized, correlating the plasma inflammatory cytokine levels to clinical ophthalmic findings [160].

Botsios et al. reported the use of anakinra for rheumatoid arthritis-associated anterior scleritis in two patients, both of whom were refractory to other immunosuppressive medications. One patient was initially treated with infliximab and methotrexate for a total of six infusions for her scleritis but experienced a decrease in visual acuity while on therapy. Anakinra, given at a dose of 100 mg/day combined with methotrexate, led to remission 8 weeks following initiation of therapy. The other patient reported had been on etanercept therapy for rheumatoid arthritis for 15 months prior to the onset of scleritis. Anakinra treatment (100 mg/day) resulted in quiescence of the scleritis following 6 weeks of therapy, with a sustained remission after 12-month follow-up [161].

Doses of anakinra range from 1–2 mg kg^{-1} day^{-1} via subcutaneous injection. In the ophthalmic literature, the dose of 100 mg/day has been used. Injection site reactions

have been the most common adverse event in long-term follow-up of rheumatoid arthritis patients [157]. In studies of anakinra in pediatric patients, injection site reactions also appear to be the most commonly reported adverse event [158, 162].

Other biologic agents

Several other biologic agents used by other subspecialty disciplines have also been described in limited case series and require further investigation.

Alemtuzumab, a humanized monoclonal antibody, which recognizes the pan-lymphocyte antigen CD52, is lymphocytotoxic and has been reported to be effective for lymphoproliferative malignancies including peripheral T cell lymphoma. Because of its ability to deplete T cells with its subsequent immunosuppressive effects, alemtuzumab has also been used for stem cell transplantation and autoimmune conditions as well [163]. Its use for severe, refractory noninfectious ocular inflammatory disease was recently described. Dick et al. reported its use in a series of ten patients with a variety of ocular inflammatory diseases including corneal graft rejection, retinal vasculitis, sympathetic ophthalmia, Wegener's granulomatosis, and Behçet's disease-associated uveitis. Eight of ten patients achieved clinical remission, allowing a decrease in their immunosuppressive medications. In the two patients with Behçet's disease and sympathetic ophthalmia, their clinical disease stabilized and became easier to control [164]. The successful use of alemtuzumab for the prevention of corneal graft rejection in a patient who had failed nine previous graft attempts despite corticosteroid, cyclophosphamide, azathioprine, and cyclosporine A has also been reported [165]. Adverse effects associated with alemtuzumab include hematologic toxicity (pancytopenia, neutropenia, thrombocytopenia, anemia) and rare cases of autoimmune hemolytic anemia. Opportunistic infection secondary to leukopenia and infusion-related illnesses consisting of fevers, rigors, and hypotension have also been reported [166].

Efalizumab, a humanized form of murine IgG1 against CD11a, the alpha subunit of lymphocyte function-associated antigen (LFA)-1, inhibits the interaction of LFA-1 with intercellular adhesion molecule (ICAM)-1, which is found on endothelial cells. LFA-1 is important in T cell trafficking into sites of inflammation via ICAM-1. Efalizumab has been approved by the FDA for the treatment of adults with moderate to severe plaque psoriasis [167, 168] and has been studied in a pilot study in patients with atopic dermatitis [169].

In EAU, expression of ICAM-1 was associated with blood–retinal barrier breakdown, immune cell adhesion, and extravasation [170]. In a mouse model of uveitis, ICAM-1 was observed on the ciliary body 6 h following induction, and LFA-1 have been observed on infiltrating lymphocytes [171]. Subsequent experiments showed that monoclonal antibodies against LFA-1 (CD11a) and ICAM-1 (CD54) inhibited the development of uveitis in a rat model and showed efficacy in the treatment of ocular inflammation [172].

The efficacy for efalizumab in the treatment of macular edema associated with noninfectious intermediate and posterior uveitis and panuveitis is currently being studied at the NEI. In the NEI treatment protocol, uveitis patients receive efalizumab at a dose of 0.7 mg/kg initially and 1-mg/kg weekly maintenance doses for a 16-week duration.

Adverse effects associated with efalizumab therapy observed during the clinical studies for psoriasis included injection reactions (i.e., headache, fever, chills, myalgias) within 48 h following the first two doses of medication. Adverse effects resulting in therapy discontinuation included pain, arthritis, and psoriasis [168]. A review of phase III clinical trials of the use of efalizumab for plaque psoriasis found no significant increase in the incidence of malignant melanoma, nonmelanoma skin cancers, and lymphoproliferative disorders in patients treated with efalizumab when compared to placebo [173]. However, in this study, the incidence of nonmelanoma skin cancers was elevated in both efalizumab and placebo-treated groups compared to external databases.

As the number of biologic immunosuppressive agents continues to increase, their use for ophthalmic inflammatory disease will likely continue. Caution is certainly warranted, as the long-term adverse effects are still unknown for many of the therapies currently being developed. Scrutiny of the basic science evidence with regard to efficacy for ocular inflammatory disease, preclinical testing, and postmarketing surveillance are also required for the treating physician. Before initiation of biologic therapy, a thorough medical evaluation is warranted, as well as a full discussion of the potential risks of immunosuppressive therapy including serious infections and secondary malignancies. The reported adverse effects as well as unknown long-term risks are also discussed so that the patients are aware of the implications of long-term systemic immunosuppressive therapy. While the TNF-α inhibitors infliximab and adalimumab and IL-2 receptor antagonist daclizumab have demonstrated promise in the treatment of ocular inflammatory disease, judicious use of these agents and future biologic therapies is necessary.

Corticosteroid delivery systems

Jaffe et al. initially reported their data from a prospective, interventional pilot trial of the fluocinolone acetonide-

sustained drug delivery device for the treatment of severe, noninfectious uveitis. The fluocinolone-sustained-release implant was designed to release corticosteroid for at least 2.5 years following implantation into the vitreous cavity. Patients treated in the initial pilot trial included Behçet's disease, idiopathic panuveitis, and intermediate uveitis. They reported stabilization or improvement in visual acuity after implantation of the device and four of seven eyes improved by three lines or more following a mean follow-up of 10 months [174].

The results of a historically controlled, multicenter trial for patients with unilateral or bilateral uveitis showed a reduction in uveitis recurrence rate from 51.4% in the 34 weeks preceding device implantation to 6.1% in the 34-week period following surgery. In addition, 87% of patients maintained or improved visual acuity with a decreased number of eyes that required topical medications, periocular injections, and systemic medications. The development of glaucoma and cataract were the most frequent complications observed with 51.1% of patients requiring topical ocular antihypertensive agents and 5.8% required glaucoma filtration surgery. In addition, 19.8% of patients showed an increase in their lens opacity, and 9.9% of the patients required cataract surgery at final follow-up [175].

The Multicenter Uveitis Steroid Treatment Trial is currently underway to compare the fluocinolone acetonide implant to standard systemic therapy for patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. Results from this study will better enable us to determine where the corticosteroid implant may fall in our current therapeutic paradigm.

A recent study evaluating the efficacy of a novel intravitreous dexamethasone drug delivery system for persistent macular edema was performed. In this study, patients with macular edema due to diabetic retinopathy, venous occlusive disease, and uveitis demonstrated similar improvements in visual acuity. At the primary endpoint assessment at 90-day follow-up, improvement in visual acuity by at least ten letters was achieved by a greater proportion of patients treated with dexamethasone 700 μg (35%) compared to patients receiving dexamethasone 350 μg (24%) and observation (13%; $P<0.001$ vs. 700-μg group; $P=0.04$ vs. 350-μg group). Injections were well tolerated in most patients; however, 11% of treated patients experienced intraocular pressure elevations of 10 mmHg or higher. Further studies evaluating this drug delivery system are underway [176].

Conclusion

In summary, a significant number of advances have been made to expand the diagnostic capabilities and therapeutic armentarium of the uveitis and ocular inflammatory specialist. The development of a standardized anatomic classification scheme for uveitis has provided a framework for future clinical outcome research. In addition, this scheme may aid the clinician in honing their differential diagnoses based on the anatomic sites of uveal inflammation for directed laboratory and radiographic testing. Ancillary testing including traditional tests such as FA and OCT continue to play a major role in the evaluation of ocular inflammatory disease. However, the advent of FAF and three-dimensional spectral OCT in clinical practice will likely assist our evaluation of ocular inflammatory diseases. Laboratory-based testing including PCR, cytokine, and chemokine evaluation has improved our ability to identify infectious etiologies and immunologic features of these conditions. As the pathogenic mechanisms that cause uveitis become apparent, medications such as the biologic agents will allow us to target specific soluble mediators of inflammation and provide improved care for patients with uveitis and other related immune-mediated ophthalmic diseases.

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