

Topics in OCULAR ANTIINFLAMMATORIES

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Intermediate Uveitis: Etiology, Diagnosis, and Treatment

LANA M. RIFKIN, MD Intermediate uveitis can be associated with a variety of infectious causes as well as systemic autoimmune diseases, most commonly multiple sclerosis and sarcoidosis. Treatment is aimed at the cause of the disease, if identified, and at the inflammation, with the goal of preventing vision loss and deleterious sequelae. Steroids are the first-line treatment for non-infectious intermediate uveitis, but patients with recurrent or chronic disease should transition to steroid-sparing therapies as soon as possible.

Intermediate uveitis (IU) can have severe consequences for vision if left untreated and can be associated with life-threatening conditions. Recognizing and appropriately treating IU is therefore of utmost importance. IU is uveitis in which the major site of inflammation is the vitreous.¹ The ciliary body and the peripheral retina may be involved, but anterior segment cells and chorioretinal inflammation are usually minimal or absent.¹ The term pars planitis refers to idiopathic IU and is only used when no infectious or systemic cause can be found.^{1,2}

The prevalence of IU has been reported as 5.9 per 100,000 individuals, with an incidence of 1.4 per 100,000 people per year.^{1,3} IU constitutes anywhere from 6.1 to 17.6% of all uveitis cases.^{4,5} In one study, nearly two-thirds of patients were female,⁶ but in general, no consistent differences in frequency between genders have been reported.^{1,7} Although IU can affect all ages, it is most frequently diagnosed when patients are in their 20s to 40s, with a mean age of approximately 35 years.^{1,6,8}

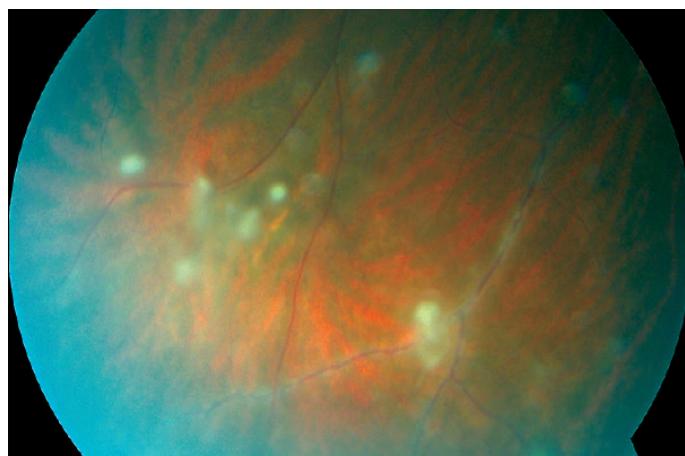


FIGURE 1 Fundus photograph showing snowball opacities and vascular sheathing, indicative of vasculitis in a patient with multiple sclerosis. (Republished from: Ozdal PC, Berker N, Tugal-Tutkun I. Pars Planitis: Epidemiology, clinical characteristics, management and visual prognosis. *J Ophthalmic Vis Res.* 2015 Oct-Dec;10(4):469-80.)

ASSOCIATION OF IU WITH OTHER DISEASES

More than 50% of IU cases are idiopathic^{6,9} and only approximately 4% of cases are associated with an infectious etiology such as syphilis¹⁰ (*Treponema pallidum*), tuberculosis (*Mycobacteria tuberculosis*) and, less frequently, Lyme disease (*Borrelia burgdorferi*) or cat scratch fever (*Bartonella henselae*). Viral etiologies of intermediate uveitis include *Herpes simplex virus*, *varicella zoster virus*, and Epstein-Barr virus.

See INSIDE for:
Dry AMD Pathobiology: Role for Antiinflammatory Therapies? by Priyatham S. Mettu, MD

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Identify infectious and non-infectious conditions associated with IU.
2. Outline the signs and symptoms of IU and preferred treatment strategies.
3. Explain leading hypotheses on AMD pathogenesis.
4. Name novel anti-inflammatory target molecules in clinical or preclinical study for AMD.

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Non-infectious IU is more common and is often associated with systemic autoimmune disease. Approximately 25% of patients with systemic sarcoidosis and 3% to 27% of patients with multiple sclerosis (MS) may develop IU at some point in their lifetime. Conversely, 2% to 10% of patients with IU will develop sarcoidosis, and 8% to 15% of patients with IU will develop MS.¹ In children younger than 7 years of age, approximately 30% of IU cases are associated with juvenile idiopathic arthritis.¹⁰ Other systemic disorders potentially associated with IU include tubulointerstitial nephritis uveitis syndrome (TINU),¹¹ Behçet's disease, Vogt-Koyanagi-Harada disease, lupus, inflammatory bowel disease, and HLA-B27 syndromes.^{1,6,12} Malignancies, including lymphoma, can also be associated with IU.²

SIGNS AND SYMPTOMS

A patient with IU will commonly present with gradual onset of blurred vision and floaters,^{2,13} and unlike anterior uveitis, will not typically experience redness, pain, or photophobia.² Young patients with a complaint of floaters should be carefully examined for signs of IU.

On examination, predominant site of inflammation in intermediate uveitis will be in the vitreous, which will present with vitritis—characterized by “snowballs,” which are aggregates of inflammatory cells.² Exudates on the pars plana are termed “snowbanks” and are the hallmark of pars planitis. Neovascularization and vasculitis may also be present (Figure 1).⁷ In some cases, inflammation—usually mild—can be seen in the anterior segment with² keratic precipitates on the cornea,⁷ anterior chamber cell, and possibly have posterior synechiae.¹⁴

DIFFERENTIAL DIAGNOSIS

A careful clinical examination and thorough patient history are the keys to a good differential diagnosis of IU. The underlying systemic cause of IU can often be gleaned from the patient's history, so it is crucial that the physician inquire about the duration of symptoms, the number of recurrences, and any other symptoms that the patient is experiencing—even if they may seem unrelated.

STATEMENT OF NEED

The control of ocular inflammation is a critical aspect of medical and surgical ophthalmic practice. Despite their side effects, antiinflammatory drugs are used to treat a very wide range of conditions throughout the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in ocular surgery, contributing greatly to patient comfort and positive outcomes.

The ocular antiinflammatory landscape is changing as research reveals more about the role of inflammation in a range of ocular conditions and as new antiinflammatory agents enter the market.^{1,2} Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or allergic conjunctivitis was viewed with alarm; today, it is accepted practice.

Although corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of the ocular anti-inflammatory armamentarium, a number of new agents with novel mechanisms of action (and new ocular drug delivery systems) have come to market or are being made ready for market.^{3,4}

As indications expand and change, and as new drugs, formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selection and use. Such protocols are also needed for routine (but nevertheless off-label) uses of corticosteroids and NSAIDs because important differences in efficacy, safety, and tolerability exist between these classes and among formulations within each of these classes.^{5,6}

By putting the latest published evidence into the context of current clinical practice, *Topics in Ocular Antiinflammatories* equips ophthalmologists to maintain competencies and narrow gaps between their actual and optimal inflammation management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

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A thorough slit lamp and dilated fundus examination is very important to detect snowballs, peripheral inflammation and vision-threatening sequelae such as neovascularization.

Laboratory and ancillary testing are useful to exclude possible causes for IU and should include a complete blood count and metabolic panel for all patients. To test for sarcoidosis, all patients should be tested for angiotensin-converting enzyme (ACE) and lysozyme.² However, for patients on ACE inhibitors, testing for ACE is not informative and does not exclude this diagnosis. A chest X-ray should be obtained to help rule out sarcoidosis and tuberculosis⁷ and detect possible malignancies. To test for TB, blood testing with an interferon-gamma release assay such as QuantiFERON Gold is recommended. Alternatively, a purified protein derivative (PPD) skin test can be performed but this necessitates a follow up visit to read the PPD and may be falsely positive in patients who have previously been immunized with BCG vaccine. To exclude syphilis, a specific treponemal test such as *Treponema pallidum* antibody or FTA-Abs is recommended.

Although multiple sclerosis can be associated with IU, not all patients with IU should be sent for magnetic resonance imaging (MRI). Those with neurologic symptoms should certainly be referred.¹⁵ At each 6-monthly follow-up visit, patients with IU should be asked about new neurologic symptoms such as tingling or numbness in the fingers or toes, any episodes of loss of speech, bowel, or bladder function or increased clumsiness. If any of these symptoms are present, an MRI is indicated.

If TINU is suspected, patients may be referred to a nephrologist for a possible kidney biopsy. Testing for inflammatory bowel disease should also be considered for patients with isolated IU, particularly for those with gastrointestinal symptoms. Genetic HLA testing may be helpful, although not diagnostic. HLA-DR15 has been associated with IU⁷ but is not specific to IU, and clinical experience suggests that it may not be informative. HLA-B27, however, may be quite helpful, particularly in a patient with lower back pain, hip pain, and back stiffness suggestive of ankylosing spondylitis.

In some cases, surgical treatment and discussion of medical treatment may be necessary, particularly when the patient is refractory to conventional medical treatment, where vitreous inflammation is especially severe, or to exclude malignancy or infection.¹ Retinoblastoma may masquerade as IU and should also be excluded, particularly in children.¹⁴

WHEN TO TREAT

Infectious causes of IU must be treated with antibiotics, antivirals, or antifungals, as appropriate. Non-infectious causes of IU may not require treatment. Patients with no loss of vision and few floaters in the absence of any signs of vision-threatening sequelae can be monitored closely with 6-monthly follow-up visits. Treatment should be re-evaluated if there is a change in symptoms or new signs of active disease.

Sequelae of under-treated IU may include cataracts, glaucoma, posterior synechiae, epiretinal membrane, etc. If sequelae that threaten vision, such as cystoid macular edema (CME) most

CORE CONCEPTS

- ◆ Most cases of IU are idiopathic, but can be associated with serious infectious or other systemic causes.
- ◆ Diagnosis is based on patient history and clinical examination.
- ◆ Further testing is useful to identify underlying causes.
- ◆ Treatment is necessary when there is significant vision loss or vision-threatening sequelae are present.
- ◆ Steroids are effective, but it is preferable to transition to steroid-sparing therapy as soon as possible.

commonly, optic nerve edema, or retinal vasculitis are present; if vision is decreased to 20/40 or less; or if symptoms interfere with the patient's daily life, then treatment is recommended.²

TREATMENT

Patients with IU should be referred to a uveitis specialist if available and may be co-managed with a rheumatologist, a nephrologist, or a dermatologist. The commonly followed, step-ladder approach proposed by Kaplan in 1984^{14,16} has recommended treatments be tried in the following order: (1) posterior subtenon depot steroid injection; (2) cryopexy (retinal cryotherapy); (3) pars plana vitrectomy; and (4) immunosuppressive therapy. Today, steroid-sparing immunosuppressive is more readily available and better understood and thus often instituted much earlier than in the past, especially in pediatric patients where the risk of cataracts and glaucoma with steroid use are quite high.

For unilateral IU, periocular steroids such as triamcinolone acetate (20-40 mg) are more effective at treating IU than topical steroids such as prednisolone acetate and are less prone to side effects than systemic steroids.¹⁷ Intravitreal steroids such as intravitreal triamcinolone or dexamethasone implants are effective,^{17,18} but carry a high risk of cataract, glaucoma, and other complications¹⁷ so should be used with caution.

Patients with bilateral IU, or with disease that is severe or refractory to treatment, should be treated with systemic steroids such as oral prednisone. It is advised to transition these patients to steroid-sparing therapy as soon as possible. The recommended dose varies but should not exceed 1 mg/kg/day, max 60-80 mg daily. Patients often require this for several weeks with slow taper to prevent quick recurrence. The goal is to control inflammation with the patient requiring less than 10 mg prednisone/day,¹⁷ and this should be achieved in less than 6 months.

Steroid-sparing medications include the immune-suppressing antimetabolites methotrexate, mycophenolate mofetil, and azathioprine.^{17,19} The calcineurin inhibitor cyclosporine can be used but has a relatively high risk of side effects.^{1,17} More recently developed treatments include tumor necrosis factor (TNF) inhibitors, such as the monoclonal antibodies infliximab and adalimumab.^{17,20} Caution is advised with these therapies in intermediate uveitis, since TNF inhibitors can potentiate demyelinating diseases, including MS, and are

contraindicated if the patient has a history of demyelinating disease or a strong family history of MS.²⁰

CONCLUSION

The definition of successful treatment of IU can be considered as achieving control of inflammation and disease with vision preserved and without vision-threatening sequelae. In most cases, inflammation can be completely controlled, but clinical experience suggests that it requires long-term treatment. Patients who are treated with systemic immunosuppression should expect treatment to last 1.5 to 2.5 years, or possibly longer. Treatment modalities are

limited by their side effect profiles and include local and systemic steroids as well as systemic immunosuppressive agents.

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RIFKIN REFERENCES continue on page 9

Dry AMD Pathobiology: Role for Antiinflammatory Therapies?

PRIYATHAM S. METTU, MD Inflammation, in particular complement and macrophages, may contribute to a number of pathogenic mechanisms in AMD. With no treatments available for dry AMD and current treatment options confined to anti-VEGF drugs for wet AMD, drugs targeting specific inflammatory pathways may represent an untapped resource for the development of new AMD therapies.

Age-related macular degeneration (AMD) is a progressive degenerative disease of the retina and the leading cause of vision loss in the elderly.^{1,2} Clinically, AMD can be categorized as either “dry” or “wet” (ie, neovascular, also referred to as exudative). AMD is characterized by an accumulation of lipid- and protein-rich deposits, called drusen that are subjacent to the retinal pigment epithelium (RPE), and by progressive damage to RPE and photoreceptor cells. In the early stages of dry AMD, patients may be asymptomatic, but many patients complain of difficulty seeing in low-light conditions, poor vision when transitioning from light to dark environments, or other visual deficits affecting activities of daily life. Geographic atrophy (GA), the advanced stage of dry AMD, is characterized by multiple foci of RPE loss and photoreceptor cell death that may grow in size and become confluent (hence, the term “geographic” or resembling a map). Patients with GA experience more pronounced visual deficits; and as GA progresses to involve the fovea, they can suffer from advanced and significant vision loss (Figure 1).

Neovascular AMD may develop at any point along the course of AMD disease and is typically characterized by the formation of aberrant choroidal new vessels (choroidal neovascularization) subjacent to the RPE and retina. In a minority of cases, neovascular AMD disease can manifest as intraretinal neovascularization (retinal angiomatous proliferation) or as a choroidal exudative disease in the absence of a discernible



FIGURE 1 Clinical color fundus photograph (CFP) and optical coherence tomography (OCT) of fovea-involving geographic atrophy (GA), the advanced stage of dry age-related macular degeneration (AMD), which causes significant central vision loss. On CFP, the area of geographic atrophy is delimited between green arrows, which corresponds to area of outer retinal thinning on OCT, delimited between red arrows. (Images courtesy of Dr. Mettu.)

neovascular lesion. Neovascular AMD can manifest as plasma leakage, hemorrhage, and fibrosis, all of which can contribute to severe and frequently rapidly progressive vision loss.^{1,2}

Risk factors for the development of AMD include advanced age, cigarette smoking, and a high-fat, high-cholesterol diet.² There is some evidence to suggest that female gender, Caucasian race, obesity, history of cardiovascular disease, hypertension, and hyperlipidemia may also be associated with increased AMD risk.^{1,2} Genetic association studies have revealed multiple genetic loci associated with development of AMD, especially genes linked to regulation of complement activity. These studies have identified increased frequency of certain gene alleles among AMD patients as compared to controls, highlighting genetic factors that modulate disease susceptibility and suggesting potential pathways that may play a role in disease pathogenesis.³

Nonetheless, the pathogenesis of dry AMD is complex and multifactorial, and involves the interplay of mechanisms in multiple tissue compartments: neurosensory retina, RPE, Bruch’s membrane, and choriocapillaris. The specific mechanisms that mediate disease onset, progression, and associated

vision loss are largely unknown; thus, there is a dearth of viable targets for development of effective treatments. There have been several disease paradigms put forth as frameworks to understand disease, which offer opportunities to develop critical new knowledge about AMD pathobiology. In this monograph, we will highlight specific pathogenic paradigms, understanding how inflammatory mechanisms may contribute to each, and we will discuss efforts “in the pipeline” to develop novel anti-inflammatories for dry AMD.

POSSIBLE MECHANISMS OF DRY AMD PATHOGENESIS

Abnormal Barrier Hypothesis

The barrier hypothesis postulates that subRPE deposit and drusen formation occurs as a result of an acquired defect in Bruch’s membrane permeability, which creates a barrier to the normal flow of nutrients and oxygen from the choroid into the RPE, and waste products from RPE into the choroid. This abnormal barrier could arise as a result of abnormal deposition of plasma-derived lipids and proteins in the inner collagenous layer of Bruch’s membrane—as a result of aging and/or oxidative injury from smoking, diet, or other factors.^{4,5} Alternatively, the abnormal barrier may arise as a result of abnormal production and secretion of lipids and proteins by the RPE, and AMD then develops as a response-to-retention of sub-RPE lipoproteins, analogous to a model of atherosclerotic disease. In either case, the development of abnormal barrier promotes worsening of membrane thickening, worsening selective impermeability, and continued accumulation of lipids and proteins in the form of subRPE deposits. The accumulation of abnormal lipids and proteins may also trigger inflammatory response—complement deposition, macrophage recruitment and retention—which may contribute to tissue injury and disease progression.

Lipofuscin/Lysosomal Failure Hypothesis

Lipofuscin is a retinal cell metabolic byproduct that accumulates in RPE cells due to an age-related failure in RPE lysosomal enzymatic degradation of phagocytosed lipid membranes and RPE-derived proteins; it contributes to RPE autofluorescence, enabling visualization of certain macular disorders, including dry AMD, on fundus autofluorescence imaging.⁴ Possible mechanisms for impaired lysosomal function include damaged or downregulated lysosomal enzymes, or loss of access to lysosomal pathways due to oxidant-mediated modification of RPE proteins or genetically altered RPE proteins leading to misfolding. Accumulation of lipofuscin may lead to further phagolysosome failure as it interrupts cellular catabolism and clearance of photoreceptor-derived lipids that have undergone oxidative degeneration. This may occur via direct damage to lysosomal pathways or indirectly by serving as a robust prooxidant substrate.² Impaired and congested phagolysosomes within RPE cells may promote oxidant-driven mechanisms of subRPE formation or may contribute to AMD disease progression via activation of RPE cell death pathways (ie, apoptosis, necroptosis) and triggering of inflammatory response.

This hypothesis is consistent with the more general “free radical theory,” which asserts that diseases of aging stem from

CORE CONCEPTS

- ◆ AMD pathogenesis involves:
 - ◆ primary retinal disease involving RPE and photoreceptors
 - ◆ lipid and protein deposition within retinal, subretinal and choroidal tissues
 - ◆ oxidative stress and ROS-related damage
 - ◆ inflammation with non-cellular (complement cascade) and cellular (ocular phagocytes) components
- ◆ Novel therapies directed against complement and macrophages are currently under development

reactive oxygen species (ROS) generation that eventually overwhelms tissues’ capacity for clearance and repair. Indeed, the macula is subject to enormous photooxidative stress from light exposure, and all AMD risk factors have been implicated in ROS generation.⁴ Further, there is histologic evidence of advanced lipid peroxidation end-products in lipofuscin (as well as Bruch’s membrane and in drusen) of patients with AMD.²

Choroidal Hypoperfusion Hypothesis

The choriocapillaris supplies oxygen and provides metabolic support to the RPE and photoreceptors. In patients with dry AMD, decreased choroidal blood flow may occur either through decreased density or diameter of choriocapillaris or through increased resistance to choroidal blood flow (eg, secondary to vascular sclerosis or increased scleral rigidity). While diminished choroidal blood flow has been observed in AMD eyes, it remains unclear whether this alteration is a primary cause of disease or a phenomenon occurring secondary to drusen and subRPE deposit formation, barrier formation, or more generalized RPE dysfunction.²

Genetic Hypotheses

Genetic and epigenetic (ie, environmental factors that modulate gene expression) mechanisms potentially underlie a number of pathogenic pathways related to the onset and progression of AMD. With rare exception, there is little evidence to suggest that dry AMD is mediated specifically by inherited primary causative mutations in proteins specific to retinal or RPE function, as with hereditary maculopathies (eg, Stargardt’s, Best disease) or retinal degenerations (eg, retinitis pigmentosa). However, there is compelling evidence that polymorphisms in general metabolic pathways that interact with outer retinal function may serve as susceptibility cofactors in AMD. This has been particularly true for multiple genetic loci related to the complement cascade, especially complement factor H (CFH). Genetic studies have also identified polymorphisms in other inflammatory molecules—unrelated or indirectly related to complement—indicating polygenic modulation of AMD pathogenesis and disease risk. These include variants of genes encoding TLR3 and TLR4 (pathogen receptors found on macrophages and other innate immune

cells); C-reactive protein (a biomarker of acute-phase inflammation); age-related maculopathy susceptibility 2 (ARMS2); and high temperature requirement factor A of serine peptidase 1 (HTRA1, a proteolytic enzyme).²

Mitochondrial Dysfunction Hypothesis

Mitochondria have long been known as the intracellular organelle responsible for energy production in the form of ATP. However, mitochondria also have other vital cellular functions, including regulation of cellular response to injury and initiation of apoptosis (eg, via cytochrome C release), modulation of protein modification and cellular transport, and retrograde mitochondrial DNA (mtDNA) signaling to nuclear transcription. Thus, mitochondria function goes beyond cellular bioenergetics and can contribute to the regulation of numerous functions, including regulation of complement, innate immunity, and angiogenesis.⁶

Mitochondrial dysfunction at the RPE and neurosensory retina can be triggered by a host of endogenous factors, including macrophage-derived oxidants, complement, immune complexes, and cytokines, and external exposures, including cigarette smoke, environmental toxicants, and blue light. This leads not only to diminished ATP production but also “electron leak” and generation of superoxide, singlet oxygen, and other oxidants that become injury stimuli, promoting lipid and protein peroxidation and damage within mitochondria and at other cellular organelles. This vicious cycle of oxidant injury triggered and perpetuated by mitochondrial dysfunction activates cellular response to injury signaling mechanisms and processes, including cortical actin cytoskeleton disassembly, cell membrane blebbing, and increased turnover of the extracellular matrix, all of which serve as biochemical mediators of subRPE deposit formation.

In healthy cells, damaged mitochondria and other oxidative stress-induced cellular debris would be removed via a process of RPE autophagy (or “self-eating”); however, in a setting of autophagy dysregulation and increased oxidative stress associated with AMD, it is postulated that damaged mitochondria that remain uncleared may contribute to local inflammatory processes in the retina.^{6,7} Histopathology studies have demonstrated damaged and fragmented mitochondria in association with drusen in eyes from AMD patients, and severity of AMD disease has been correlated with the extent of damaged RPE mtDNA.

COMPLEMENT

The complement cascade is vital for host defense against pathogens and for turnover and clearance of damaged cells. In 2005, a series of high-profile, genome-wide association studies revealed a link between polymorphisms in complement factor H (CFH) and increased susceptibility to dry AMD.⁸⁻¹⁰ As CFH serves to regulate complement activation, this raised the hypothesis that increased complement activation may play a role in dry AMD pathogenesis. Previous to that, histopathologic studies revealed deposition of complement components within the choroid, Bruch’s membrane, and the subretinal space of eyes with AMD, and these were subsequently corroborated by findings of complement in association with subretinal deposits

in mouse models. Since that time, additional polymorphisms in complement factor I, complement factor B, and C3 have been identified in association with dry AMD. However, the mechanism(s) by which the complement cascade might influence development or progression of AMD remains unknown.

One possibility is that activation of the alternative pathway of the complement system triggers formation of the membrane attack complex (MAC), a conglomeration of complement components assembled into a transmembrane channel, causing osmotic lysis of the target cell. Aberrant MAC formation in the setting of AMD may inappropriately target RPE cells and photoreceptors (and possibly choroidal endothelial cells), leading to cell death and progressive disease.¹¹

Another possibility is that C3a and C5a—cleavage products of complement—may act as anaphylatoxins, increasing vascular permeability and recruiting inflammatory cells such as leukocytes and macrophages to the site of disease, which then promote progression of dry AMD and/or conversion to neovascular AMD.¹¹

MACROPHAGES

Macrophages, cells of the innate immune system, may modulate the severity of AMD disease depending on their activation state. Blood-derived macrophages are recruited from the systemic circulation as monocytes and directed to Bruch’s membrane, RPE, and the retina by inflammatory cytokines at the site of disease. On the one hand, macrophages that are primed for reparative function (as well as microglia, the resident immune cells of the retina) may act as scavengers to remove cellular debris, remove inflammatory stimuli, promote drusen clearance, and healthy tissue repair, thereby limiting progression of disease. On the other hand, macrophages may be pro-inflammatory, producing cytokines and effector molecules (TNF- α , IL-6, IL-1b) that promote nonlethal or lethal injury to RPE cells and photoreceptors, promoting disease progression.^{12,13} Evident within the neurosensory retina, subretinal space, and subRPE space in various stages of dry AMD by histopathology, macrophages may also cause vision impairment through deleterious effects on retinal circuitry. Possibilities include interruption of the normal visual cycle between RPE and photoreceptors in the subretinal space; secretion of effector molecules that disrupt synaptic transmission between photoreceptors and bipolar cells; or compromise to Muller cell processes that provide perisynaptic support within the inner and middle retina.

Macrophages also contribute to neovascular AMD, particularly the subset of disease that is resistant to anti-VEGF therapies. Treatment-resistant disease occurs most frequently among eyes with CNV lesions with branching arterIALIZATION and perivascular fibrosis, which animal studies show is mediated by nonclassical or reparative macrophages that secrete fibrogenic factors (TGF- β , IGF-1, FGF, others). Glucocorticoids do not diminish the biologic activity of the macrophage subset (and in fact, may upregulate their activity), which perhaps explains why adjunctive corticosteroids have not been shown to be effective for patients with anti-VEGF resistant neovascular AMD.¹⁴

Novel macrophage-targeting therapies—several of which

are in early stages of development—would offer an attractive alternative or adjunct to anti-VEGF therapies for poorly responsive wet AMD patients.

NLRP3 INFLAMMASOME

The NLRP3 inflammasome is a multimeric complex of cellular proteins that assembles in response to specific danger signals (eg, dsRNA, cytoplasmic DNA), integrating cellular responses to various injury stimuli (eg, oxidants) and inducing an inflammatory response in the form of cytokine (eg, IL-18, IL-1 β) production and secretion. Previously described in myeloid cells including macrophages and microglia, the NLRP3 inflammasome has recently been described and characterized in RPE cells. Several studies, including from Ambati and colleagues have demonstrated that NLRP3 activation in RPE, particularly by accumulation of Alu RNA, is associated with pyroptosis and lethal injury of RPE cells and photoreceptor loss in mouse models of dry AMD, with corroborative features present in histopathology of human dry AMD.^{15,16} On the other hand, other investigators have suggested that activation of NLRP3, particularly in macrophages, may ameliorate AMD disease severity.¹⁷ Further study is needed to characterize the specific roles of NLRP3 inflammasome in various stages of AMD disease, but modulation of NLRP3 inflammasome activity could represent a therapeutic target in dry AMD.

NEW AND IN-DEVELOPMENT INTERVENTIONS

While a comprehensive review of drugs in development for the treatment of AMD is beyond the scope of this article, several novel drugs “in the pipeline” targeting complement or macrophages are highlighted below.

Complement Inhibitors

Complement factor C3 is a central component of the complement cascade that may contribute to GA, so there is strong rationale for inhibition of C3 for the prevention or reduction of RPE and photoreceptor cell death in AMD.¹⁸ Two phase 3 trials (DERBY and OAKS) are underway for C3 inhibitor APL-2 (Apellis Pharmaceuticals, Crestwood, KY), a pegylated cyclic peptide administered once- or bi-monthly by intravitreal injection, to reduce progression of GA.¹⁹ A phase 2 trial (FILLY) showed that APL-2 given monthly or bi-monthly reduced disease progression by 29% ($P = 0.008$) and 20% ($P = 0.067$) respectively at 12 months compared with control (sham injections), with more pronounced effect in the second 6 months of treatment. A higher rate of activated exudative AMD was observed in patients receiving APL-2; however, overall visual outcomes were unaffected.²⁰ APL-2 is also in phase 2 trials for the treatment of neovascular AMD.

Avacincaptad pegol (Zimura; Ophthotech, Princeton NJ), an inhibitor of complement factor C5, is currently in phase 2 clinical trials for the treatment of GA. An open-label phase 2a trial is also underway for avacincaptad pegol as an adjunct to anti-VEGF therapy for the treatment to neovascular AMD.²¹

CD59, also known as MAC inhibitory protein (MAC-IP) is a membrane-bound protein that inhibits formation of MAC

transmembrane channel. HMR59 (Hemera Biosciences) is an adeno-associated virus vector (AAV2) expressing a soluble form of CD59 (sCD59), delivered via single intravitreal injection. A Phase 1 study is underway to assess safety of HMR59 in patients with dry AMD and GA.

Development has ceased for intravitreal anti-complement factor D lampalizumab (Roche/Genentech, San Francisco CA) and intravenous anti-C5 eculizumab (Alexion Pharma, New Haven CT), following failure to meet clinical endpoints during respective phase 3 and phase 2 clinical trials for treatment of GA.^{22,23}

Therapies Against Macrophages and Inflammasome

TMi-018 (Translatum Medicus Inc., Toronto CA) is a transcriptional modulator of macrophage activation state, currently in pre-clinical development (short-acting and slow-release formulations) for dry AMD and GA.²⁴

Nucleoside reverse transcriptase inhibitors (NRTIs) have been shown to prevent atrophic disease in mouse models of AMD via downregulation of NLRP3 inflammasome activity in several studies by Ambati and colleagues.²⁵ Work is underway to develop optimized NRTI derivatives for the treatment of dry AMD (Inflammasome Therapeutics).²⁶

Other Immunomodulatory Therapies

Immunosuppressive agent sirolimus, which inhibits T and B cells and may also have anti-macrophage activity, failed its phase 2 trial of intravitreal treatment of GA.²⁷ Studies of sirolimus in the treatment of noninfectious uveitis have been more successful and are ongoing. Research has also halted development of topical ocular antiangiogenic and anti-inflammatory molecule squalamine (Ohr Pharmaceuticals, New York, NY) after failing to meet its primary endpoint in a phase 3 trial when administered adjunctively with anti-VEGF therapy in the treatment of wet AMD.²⁸

CONCLUSION

The lack of available efficacious therapies for dry AMD highlights the importance of new knowledge about specific disease-mediating mechanisms. An increasingly appreciated role for inflammation in AMD pathogenesis, in particular complement-, macrophage-, and inflammasome-mediated pathways, may reveal new targets for drug development. Clinical trials for novel anti-inflammatory drugs targeting complement and macrophages, if successful, will validate specific targets and provide additional insights into AMD pathobiology for future drug development initiatives.

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1. TMi-018, in development for treatment of dry AMD, targets which of the following?
 - A. Complement
 - B. Macrophages
 - C. Inflammasome
 - D. None of the above
2. The most common cause of vision loss in IU is:
 - A. Cystoid macular edema
 - B. Retinal vasculitis
 - C. Cataract
 - D. Glaucoma
3. Among the following choices, the most likely diagnosis in a 65-year-old patient who has normal visual acuity (ie, 20/20) but complains of difficulty reading in low light is:
 - A. Exudative AMD
 - B. Geographic atrophy
 - C. Early dry AMD
 - D. Lysosomal storage disease
4. Non-infectious IU is most often associated with:
 - A. Sarcoidosis
 - B. Multiple sclerosis
 - C. Lupus
 - D. A and B
5. Studies have uncovered a genetic link to AMD for which of the following immune/inflammatory components?
 - A. Complement factor H
 - B. C-reactive protein
 - C. ARMS2
 - D. All of the above
6. Which of the following is NOT a risk factor for AMD?
 - A. Mediterranean diet
 - B. Smoking
 - C. Age
 - D. Genetic predisposition
7. Failure of phagolysosomal function is a central mechanism in which paradigm of AMD pathogenesis?
 - A. Barrier hypothesis
 - B. Choroidal hypoperfusion
 - C. Lipofuscin hypothesis
 - D. Mitochondria hypothesis
8. Effective steroid sparing medications include:
 - A. Mycophenolate mofetil
 - B. TNF inhibitors
 - C. Methotrexate
 - D. A, B, and C
9. MRI is indicated:
 - A. For all patients with IU
 - B. For patients with IU and neurologic symptoms
 - C. For patients with IU and suspected sarcoidosis
 - D. Never
10. A hallmark of IU is:
 - A. Photophobia
 - B. Ocular pain
 - C. Snowballs in the vitreous
 - D. Redness

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