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LEO Clinical Topic Update

Uveitis

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American Uveitis Society

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Introduction

This Clinical Topic Update summarizes the important changes that have occurred in the field of ocular inflammatory disease over the last 5 years, including dramatic changes that have occurred relating to acquired immunodeficiency syndrome (AIDS) as a result of new antiretroviral and anti-cytomegalovirus (CMV) therapies and diagnostic assays. Changes have also occurred in the diagnosis, characterization, and treatment of noninfectious uveitis. Several anti-inflammatory agents have recently received FDA approval for the treatment of systemic inflammatory disease, and these are discussed because they may prove useful for the treatment of noninfectious uveitis.

AIDS-Related Disease

Cytomegalovirus Retinitis

Changes in the Clinical Picture. The classic presentation of cytomegalovirus retinitis is a retinal inflammation with areas of retinal necrosis and scattered hemorrhage. There are often white spots at the leading edge of the retinitis, and there may be an accompanying periphlebitis. A second form of CMV retinitis may also be seen, the so-called granular form. This form of retinitis is more common in the retinal periphery and in previously treated patients. It is slightly slower in its rate of progression than the hemorrhagic form. Unilateral CMV retinitis becomes bilateral in approximately 50% of untreated patients.

Until recently, the incidence of CMV retinitis was 20% per year in AIDS patients with CD4 counts below 50 per cubic mm, and the lifetime probability was 30%.[1] It was seen almost exclusively in patients with CD4 counts of less than 200 per cubic mm and was most common in patients with CD4 counts of less than 50 per cubic mm.[2] This changed dramatically with the introduction of highly active antiretroviral therapy (HAART). This therapy, which consists of combinations of antiretroviral medications, has dramatically changed the face of AIDS, and the incidence of CMV retinitis has markedly decreased. For example, Palella and colleagues reported an 83% decline in the incidence of the three major opportunistic infections (CMV retinitis, *Pneumocystis carinii* pneumonia, and *Mycobacterium avium* complex disease) from 1994 to 1998.[3]

The clinical presentation of CMV retinitis is also changing. It is now not uncommon to diagnose CMV retinitis in patients with higher CD4 counts, usually shortly after starting HAART but before complete immune reconstitution.[4] The appearance of CMV retinitis may be more subtle or indolent in patients on HAART, with observable progression in the absence of obviously active borders. Fundus photography is particularly helpful in following these patients, because it is more sensitive than clinical examination alone.[5] In addition, a mild to moderate vitreous inflammatory reaction is sometimes seen, in contrast to the quiet vitreous that was once the rule.

Another new clinical entity is that of immune recovery uveitis. This inflammation may develop in a significant number of patients on HAART with

active or inactive CMV retinitis.[6] Patients may develop vitritis, papillitis, disc or macular edema, and epiretinal membranes.[7–9]

The diagnosis of CMV retinitis used to mandate lifelong anti-CMV therapy. This therapeutic protocol has also changed. There is evidence that HAART therapy may restore CMV-specific CD4-positive lymphocyte responses.[10] A number of investigations have documented a lack of recurrence of CMV retinitis after discontinuation of anti-CMV therapy in HAART patients who have a prolonged elevation of CD4 count and a decrease in HIV viral load.[11–14] However, there is no consensus as yet regarding when anti-CMV therapy may be discontinued.

It is important to realize that HAART is not a panacea. There is evidence that patients with an initial decrease in human immunodeficiency virus (HIV) viral load to undetectable levels will have measurable rises within 1 year.[15] Some of the patients who experience virological failure may continue to have sustained CD4 counts.[16] Other patients, however, completely fail HAART because of viral resistance, noncompliance, or other host factors. Thus, while the incidence of CMV retinitis has markedly decreased, it has not yet gone the way of smallpox. Patients with AIDS and low CD4 counts are still at risk for CMV retinitis and other opportunistic infections.

Advances in Laboratory Testing. Several assays are now commercially available to quantitate CMV DNA in peripheral blood. Polymerase chain reaction (PCR) testing may be used to confirm a clinical diagnosis of CMV disease. PCR has high positive predictive value in determining which patients with HIV will develop CMV end-organ disease.[17–19] Antigenemia testing, which uses monoclonal antibodies to CMV protein, also has good positive predictive value.[20,21] Urine and blood cultures for CMV may be performed, but these have low positive predictive value for the development of CMV disease.[22,23] A molecular diagnostic test based on quantitative solution hybridization is also available; it has excellent positive predictive value. Using this technique, Tufail and colleagues demonstrated that an increase in peripheral CMV DNA in patients with CMV retinitis was followed by reactivation of retinitis or development of extraocular CMV disease in all cases. As with the other methods described, however, the converse was not true: CMV DNA levels did not always rise before reactivation of CMV retinitis.[24] Therefore, while the tests described above may be useful for determining which subsets of AIDS patients are at risk for the development of CMV end-organ disease, they cannot be relied upon to determine reactivation of CMV retinitis. Because reactivation may occur without elevation in blood levels of CMV, regular clinical examination by an ophthalmologist is still required.

Advances in Management. There have been many changes in the *systemic therapy* of CMV retinitis, because of both the changing nature of the disease and the availability of new therapeutic options. All of the systemic medications for the treatment of CMV retinitis also decrease the risk of contralateral eye involvement and systemic CMV infection.

Until recently, intravenous ganciclovir (Cytovene) and foscarnet (Foscavir), two virostatic drugs, were the only available therapies for CMV retinitis.

Ganciclovir is generally administered at a dose of 5 mg per kg bid for a 14- to 21-day induction, followed by 5 mg per kg per day maintenance, continued indefinitely or until there is adequate immune recovery. Foscarnet is administered at a dose of 90–120 mg per kg bid for a 14- to 21-day induction, followed by 90–120 mg per kg per day maintenance, also continued indefinitely or until there is adequate immune recovery. The dosage of both of these agents may need to be modified based on renal function. The principal toxicity of ganciclovir is hematopoietic, with the development of neutropenia and thrombocytopenia. Filgrastin (Neupogen), a granulocyte-stimulating factor, has been helpful in managing these side effects. The most significant side effect associated with foscarnet is the development of renal insufficiency.

Despite daily IV maintenance therapy, recurrence of CMV retinitis is the rule rather than the exception for patients treated with intravenous ganciclovir or foscarnet. The median time to progression of CMV retinitis activity on either of these therapies is 2 months in patients without immune recovery. Because of this recurrence, long-term IV ganciclovir or foscarnet is no longer the gold standard for the treatment of CMV retinitis.

The combination of IV ganciclovir and foscarnet was studied in a randomized, multicenter, controlled clinical trial, the CMV Retinitis Retreatment Trial (CRRT). Although mortality rates were similar among groups and visual outcomes did not differ, retinitis progression was less in the group treated with a combination of ganciclovir and foscarnet than in the other two groups, which were treated with ganciclovir or foscarnet alone.[25] Despite this advantage, combination therapy is not often used because of significant side effects and patient preference.

Cidofovir (Vistide) is an acyclic nucleotide that inhibits CMV replication by competitive inhibition of viral DNA polymerases. It is FDA-approved for intravenous use, and it has a longer half-life than other available intravenous drugs.[26] The induction dose is 5 mg per kg IV once a week, and maintenance therapy is given IV every 2 to 3 weeks. The drug does not require the use of an indwelling central line and offers significant benefits to the patient in terms of convenience. Its main drawback is a risk of significant nephrotoxicity, which is more severe than that observed with foscarnet. The nephrotoxicity may be lessened by strict adherence to appropriate hydration and coadministration with probenecid, which protects the renal tubules. Unfortunately, probenecid often causes a flu-like illness that may decrease patient compliance with the regimen. A lower dose of cidofovir (3 mg per kg) may be used in select patients. IV cidofovir may also result in fibrinous iridocyclitis and irreversible ocular hypotony,[27,28] which is worse if probenecid is omitted.

Ganciclovir is now available in an oral form. The dose initially studied was 1 g po tid given after stabilization of retinitis with 3 weeks of IV ganciclovir induction.[29] Recent data, however, suggest that a 2 g tid oral dose achieves a serum concentration comparable to that seen with IV infusion,[30] and preliminary data suggest that this dose is more effective than the lower oral dose with an efficacy approaching that of IV ganciclovir. Most clinicians currently use oral ganciclovir for secondary prophylaxis in patients receiving local therapy, reserving its use as primary therapy for patients with some immune reconstitution.

A new oral agent, valganciclovir, is undergoing clinical trials. It is given orally bid for induction followed by once-a-day maintenance therapy. Preliminary data suggest that its efficacy is at least as good as that of IV ganciclovir.[31]

With regard to developments in *local therapy* of CMV retinitis, both ganciclovir and foscarnet may be administered by means of intravitreal injection through the pars plana, although this is an off-label use of these agents. Ganciclovir is typically administered once weekly for maintenance, usually at a dose of 2000 µg per injection. Foscarnet is administered weekly in doses of up to 2400 µg. The intravitreal injection is performed using sterile technique and local or topical anesthesia. A short 27- or 30-gauge needle is used to inject 0.05 to 0.1 cc of drug. The procedure is usually well tolerated, with only minimal rise in intraocular pressure. This route of administration may be used for temporary treatment in a patient awaiting a ganciclovir implant or in cases where long-term therapy is not anticipated. It is usually not the treatment of choice for long-term therapy because of inconvenience and the risk of endophthalmitis, cataract, and retinal detachment engendered with repeated intravitreal injection. Local therapy alone does not decrease the risk of contralateral eye involvement or systemic CMV infection.

Fomivirsen sodium (Vitravene) is an oligonucleotide that is complementary to human CMV major immediate early region mRNA, and it is thus able to interfere with the synthesis of important CMV proteins. It was FDA-approved for the treatment of CMV retinitis in August 1998 and is the first antisense compound to receive approval. Fomivirsen has the advantage of an absence of cross-resistance with the other anti-CMV agents and may be administered intravitreally every 2 to 4 weeks. It may result in more ocular inflammation than ganciclovir or foscarnet, although it does not cause the severe fibrinous iridocyclitis associated with cidofovir. It is a reasonable treatment option for patients with CMV retinitis that is resistant to the nucleoside and nucleotide agents and in patients with rising CD4 counts who may not require prolonged therapy. Used alone, fomivirsen does not decrease the risk of contralateral or systemic CMV infection.

Cidofovir has been used intravitreally in doses of 15 to 20 µg for the treatment of CMV retinitis. It may be administered less frequently than the other agents, usually approximately every 6 weeks. Although the drug is able to arrest retinitis very effectively, it may result in significant fibrinous iritis and hypotony.[32] The package insert supplied with the drug specifically prohibits its use intravitreally, and its use is therefore not recommended unless every other possible treatment option has been exhausted.

A sustained-release intraocular device is available that releases ganciclovir over a period of approximately 8 months. It is very effective in treating and preventing progression of CMV retinitis, with a longer time to progression than systemic therapy.[33] As with other local therapies, it does not prevent the development of retinitis in the fellow eye nor the development of systemic CMV.[34] Oral ganciclovir is often administered concurrently if there are no contraindications, in order to decrease the risk of contralateral and extraocular CMV disease. Placement of the ganciclovir implant is associated with an increased risk of early retinal detachment, but with longer follow-up there is no

difference in retinal detachment rates between patients treated with IV ganciclovir or with the implant.[33] Thus, while the surgical procedure and disruption of the vitreous may be associated with an increased risk of retinal detachment, this risk seems to be counterbalanced by the better control of retinitis obtained with the implant. The combination of the ganciclovir implant and secondary prophylaxis with an oral agent is the regimen of choice for most patients with ganciclovir-sensitive CMV retinitis and no immediate promise of immune reconstitution.

Other AIDS-Related Eye Disease

Toxoplasmosis. Toxoplasmic retinitis presents a diagnostic challenge in immunosuppressed patients, because it may be clinically indistinguishable from CMV retinitis.[35] Clinical findings that suggest the diagnosis of toxoplasmosis rather than CMV include ocular pain and redness, dense retinal opacification with smooth borders, granulomatous anterior chamber reaction, dense vitreous reaction, and absence of retinal hemorrhage. Toxoplasmosis may also present as a miliary retinitis in AIDS patients, with multiple 100- to 500-micron-sized lesions scattered throughout the posterior pole.[36]

Antibody titers are often not helpful in cases of suspected toxoplasmosis, because they may be positive in the absence of active disease. They may also become negative in the presence of active ocular infection in severely immunosuppressed patients.[37] Although toxoplasmosis must be in the differential diagnosis of a patient with hemorrhagic retinitis, it occurs in only about 1% to 3% of AIDS patients.[38] Any patient diagnosed with ocular toxoplasmosis should be evaluated for CNS toxoplasmosis.

Multifocal Choroiditis. Numerous organisms may cause multifocal choroiditis in AIDS patients. Etiologic agents that have been identified include *Cryptococcus neoformans*, *Pneumocystis carinii*, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*, *Histoplasma capsulatum*, *Candida* species, *Aspergillus fumigatus*, and *Toxoplasma gondii*.[39] The lesions are usually creamy white, 200 to 3000 µm in size, and are commonly scattered through the posterior pole. The diagnosis of the specific etiologic agent responsible usually cannot be made based on the ocular clinical picture alone. Diagnosis is made by correlation with the systemic clinical picture, and lumbar puncture may be required. On rare occasions uveal biopsy may be required. Similar lesions may also be caused by intraocular lymphoma.

Rifabutin-Associated Acute Anterior Uveitis. Rifabutin (Mycobutin), a drug that has been used for prophylaxis and treatment of *Mycobacterium avium* complex in AIDS, has been associated with a uveitic syndrome. Patients with rifabutin-associated uveitis may present with pain, redness, photophobia, and significant anterior chamber reaction. Hypopyon and severe vitritis may also be present. This noninfectious uveitis must be differentiated from infectious endophthalmitis, which can have a similar presentation.[40]

Non-AIDS-Related Uveitis

Advances in Diagnosis and Characterization

Pars Planitis and Multiple Sclerosis. Multiple sclerosis (MS) was diagnosed in 15% of patients in one series of 54 patients with pars planitis.[41] The HLA-DR2 haplotype was found in 67.5% of these patients, as opposed to 20% of controls and 50% to 70% of patients with MS.[42] In another series of 37 patients with pars planitis, 16.2% developed MS. The HLA-DR15 allele, a subtype of HLA-D2, was significantly associated with pars planitis in these patients (present in 46.9% of patients with pars planitis and in 23.6% of controls).[43] These data suggest that a gene product of HLA-DR15 or a genetic linkage to this locus may be important in the pathogenesis of both pars planitis and MS.

Multifocal Choroiditis and Sarcoidosis. In a series of 10 patients with peripheral chorioretinal lesions and vitritis that was reported in 1994, seven had noncaseating granulomas on conjunctival biopsy. Six of the seven were older than age 58, and four of the seven had either elevated serum angiotensin-converting enzyme levels or abnormal chest x-rays consistent with sarcoidosis. These findings suggest that sarcoidosis may be a cause of multifocal choroiditis, especially in older patients.[44]

Confirmation of the diagnosis of sarcoidosis as a cause of uveitis remains difficult. In patients with presumed ocular sarcoidosis but nondiagnostic chest x-ray, the combination of serum angiotensin-converting enzyme elevation and abnormal whole-body gallium scanning increases diagnostic specificity, although it does not increase diagnostic sensitivity.[45] Computed tomography (CT) of the chest may be more sensitive than chest x-ray and has revealed sarcoid-related lymphadenopathy in elderly patients with normal chest x-ray.[46] There are still many patients who clinically appear to have ocular sarcoidosis, but in whom there is no evidence of systemic disease. In some of these patients, sarcoidosis will present systemically years after the initial ocular disease.

Toxoplasmosis. Indocyanine green angiography of patients with active toxoplasmosis may reveal multiple hyperfluorescent satellite spots that are not detected clinically or with fluorescein angiography.[47] Because these lesions fade with treatment, indocyanine green angiography may be particularly useful in patients with silent progression of toxoplasmosis scars, revealing clinically invisible active satellite lesions.[48]

Ultrasound Biomicroscopic Imaging. The ultrasound biomicroscope (UBM), which has lateral resolution approaching 20 µm, can provide useful information in patients with uveitis.[49] It can provide anatomic detail of anterior segment structures not well seen because of media opacities, or it can image structures that are not normally well seen clinically. For example, it may be helpful in cases of pseudophakic iridocyclitis, allowing visualization of IOL haptics that are impinging on the ciliary body. The UBM is also useful for evaluating cystic lesions of the iris and ciliary body.[50] It can provide information about the pars plana in patients without clear media,[51] and about the pars plicata, which is not

typically seen clinically.[52] Ciliochoroidal detachments not seen clinically may be seen on UBM.[53]

Laser Flare-Cell Photometry. The laser flare-cell photometer measures the intensity of back-scattered light produced in the anterior chamber by a helium neon laser beam. A photomultiplier detects back-scattered photons and the data are computer analyzed. Flare intensity is proportional to the amount of anterior chamber protein, and particles between 9 and 12 µm can be detected. At present, the Kowa MC-1000 laser flare-cell photometer has been shown to be accurate for measuring anterior chamber flare but less accurate for counting cells. Because of this problem and the device's high cost, this instrument has been used for research but has not yet found a role in the clinical practice of uveitis.[54]

Chorioretinal Biopsy. Chorioretinal biopsy may be used as a diagnostic tool in cases of sight-threatening lesions that are not responsive to therapy; suspected malignancy; and possible infectious chorioretinitis that cannot be diagnosed by noninvasive means. The most common complication of the procedure is progression of lens opacification. Chorioretinal biopsy may provide specific diagnostic information in a case where vitreous biopsy may show only nonspecific inflammation. Chorioretinal biopsy specimens should be processed for light and electron microscopy, immunohistochemistry, and tissue culture.[55]

Latanoprost-Associated Anterior Uveitis and Cystoid Macular Edema. Latanoprost (Xalatan), a prostaglandin analog, has been demonstrated to be very effective in lowering intraocular pressure.[56,57] There have been a number of reports, however, that suggest that its use is associated with the development of anterior uveitis and cystoid macular edema,[58,59] although many of the patients in these reports had other reasons to have cystoid macular edema, such as previous cataract surgery or uveitis. [60,61] While it is still not conclusively proven that latanoprost can cause cystoid macular edema, the clinician should be aware that it is a possibility, especially in patients with preexisting uveitis or other predisposing factors for the development of CME.

Advances in Management of Infectious Uveitis

Endogenous Endophthalmitis. Metastatic or endogenous endophthalmitis is a rare but potentially devastating condition. Any new case of hypopyon uveitis in which the vitreous is hazy and the fundus cannot be adequately evaluated should be considered for aqueous and vitreous tap, as well as for intraocular injection of antibiotics. While it is most common in patients with underlying medical problems—including diabetes mellitus, gastrointestinal disorders, hypertension, cardiac disorders, and malignancies—endogenous endophthalmitis can occur in patients without underlying illness.[62] Gram- positive organisms are usually implicated. The role of intraocular antibiotics as an adjunct to systemic therapy has not yet been clearly defined.

Early Postoperative Endophthalmitis. The role of immediate pars plana vitrectomy and intravenous antibiotics in the management of bacterial endophthalmitis after cataract surgery has been addressed by a multicenter, randomized, controlled clinical trial, the Endophthalmitis Vitrectomy Study.[63] A total of 420 patients with endophthalmitis that occurred within 6 weeks of cataract surgery or secondary IOL implantation were studied. Systemic antibiotics did not result in significantly better visual acuity, nor did immediate pars plana vitrectomy when the initial visual acuity was detection of hand motion or better. When inflammation at presentation was severe enough to decrease visual acuity to light perception only, however, immediate pars plana vitrectomy led to a significantly better final visual outcome.[63]

While there are many potential drug combinations for intravitreal drug therapy of acute postoperative endophthalmitis, the currently accepted approach is to use two drugs, one to cover Gram-positive organisms and one to cover Gram-negative organisms. Vancomycin is the traditional drug of choice for Gram-positive coverage. It is the only agent tested to which all Gram-positive species in the Endophthalmitis Vitrectomy Study were susceptible.[64] The development of vancomycin-resistant strains of staphylococcal and streptococcal species has prompted the Centers for Disease Control (CDC) to recommend reserving the use of vancomycin for the treatment of serious infections caused by beta- lactam-resistant Gram-positive microorganisms.[65]

Cefazolin has activity against many Gram-positive organisms. However, in a rabbit model of *Staphylococcus aureus* endophthalmitis, cefazolin was less effective than vancomycin[66] and clinical resistance of Gram-positive organisms to cefazolin occurs frequently.[67] In light of the absence of data suggesting an effective alternative to vancomycin and the potentially devastating consequences of endophthalmitis, vancomycin remains the agent of choice for the coverage of Gram-positive organisms in cases of postoperative endophthalmitis. Intravitreal injection of aminoglycosides for Gram-negative coverage has been associated with macular infarction. Ceftazidime is bactericidal against the majority of Gram-negative bacteria and appears to result in less retinal toxicity than the aminoglycosides.[68] The combination of intravitreal vancomycin and ceftazidime is therefore the most commonly used combination for initial empirical antibiotic therapy of endophthalmitis.[69–71]

Late Postoperative Endophthalmitis. Chronic iridocyclitis occurring months to years after uncomplicated cataract surgery may be caused by indolent organisms such as *Propionibacterium acnes*, *Staphylococcus epidermidis*, *Corynebacterium* species, and some fungi.[72,73] *P acnes* endophthalmitis is caused by viable organisms within lens capsular remnants. The typical presentation is that of anterior chamber reaction and low-grade anterior vitreous inflammation, frequently with focal areas of white opacification within the capsular bag, developing between 2 and 10 months after surgery. The inflammation may initially respond partially or transiently to corticosteroids. It then recurs and frequently becomes granulomatous in nature, with large keratic precipitates and even hypopyon. In some patients, injection of clindamycin or vancomycin into the posterior chamber may clear the infection,[74] although removal of the organisms with total capsulectomy and IOL exchange may be required.[75]

Toxoplasmic Retinochoroiditis. Standard therapies for toxoplasmosis (including pyrimethamine, clindamycin, and sulfonamides) are not active against *Toxoplasma* tissue cysts, and therefore do not prevent disease recurrence. They are also quite toxic. The primary side effect of pyrimethamine is significant bone marrow toxicity, which often limits its use. Clindamycin is better tolerated but is associated with a risk of development of pseudomembranous colitis.

Two newer drugs have been investigated for the treatment of toxoplasmosis. These two agents, azithromycin (Zithromax) and atovaquone (Mepron), both have been demonstrated to have in vitro and in vivo efficacy against the cyst forms of *Toxoplasma gondii*. Azithromycin is an azalide antibiotic that has been demonstrated to be an effective treatment for ocular toxoplasmosis in immunocompetent patients. A 500 mg loading dose followed by 250 mg daily is well tolerated but does not prevent recurrences.[76] Atovaquone was also studied in a cohort of immunocompetent patients with ocular toxoplasmosis.[77] In this series, patients were treated with 750 mg of atovaquone po qid for 3 months. All patients had favorable response, but recurrence was not prevented. Although these two new agents held great promise because of their reported efficacy against cyst forms, they may not be any more effective than the standard therapies. Atovaquone has been associated with the development of rashes, nausea, diarrhea, and headache, as well as with anemia, neutropenia, and abnormal liver function. Azithromycin has been rarely associated with serious allergic reaction, including angioedema, anaphylaxis, and Stevens-Johnson syndrome. It has also been reported to cause cholestatic jaundice. More common side effects include nausea, vomiting, and diarrhea.

Medical Therapy of Noninfectious Uveitis

Systemic therapy is often necessary for the control of noninfectious ocular inflammation. When a decision is made to use systemic therapy, alternatives include nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive therapy.

Corticosteroids have long been the mainstay of anti-inflammatory treatment. These drugs are not without serious side effects, however. Osteoporosis, peptic ulcer disease, Cushing's syndrome, diabetes, cataract, glaucoma, and increased susceptibility to infection may all result from the prolonged use of corticosteroids.[78] For these reasons, many physicians prefer to limit the use of oral corticosteroids to a maximum of 6 to 12 months and then to switch to or add other immunosuppressive agents if the patient requires prolonged systemic treatment.

Cyclosporine. Cyclosporine is a cyclic polypeptide that inhibits lymphokine production and suppresses T-cell activation and recruitment. It may be of value in the treatment of diseases such as Behçet's disease, Vogt-Koyanagi-Harada syndrome, and sympathetic ophthalmia.[79,80] It has been demonstrated to be a safe and effective therapy for sight-threatening uveitis in children.[81] Cyclosporine is given orally, often beginning with doses of 5 mg per kg per day and reducing the dose once a therapeutic effect is seen. A new form of cyclosporine, the microemulsification formulation Neoral, has greater and more consistent

absorption than the original form (Sandimmune).[82] Side effects include renal toxicity, hypertension, gastrointestinal disturbance, hepatotoxicity, muscle cramps, malaise, headaches, hypertrichosis, gingivitis and gingival hyperplasia, and oral ulcers.[83,84] Cyclosporine is usually used as a corticosteroid-sparing agent rather than as monotherapy, because the dose required when it is used alone may be profoundly nephrotoxic.

A variety of drugs alter blood levels of cyclosporine. Agents that increase blood levels include ketoconazole (Nizoral), oral contraceptives, doxycycline, erythromycin, and calcium channel blockers. Barbiturates, rifampin, and phenytoin may decrease plasma concentrations. Any drug that increases the blood levels of cyclosporine may increase side effects, and those that decrease blood levels may decrease efficacy.

Diclofenac, aminoglycosides, amphotericin B, and trimethoprim may all potentiate the nephrotoxicity of cyclosporine, and nifedipine may augment gingival hyperplasia. There have also been recent reports that cyclosporine can promote cancer progression by means of a direct cellular effect that is independent of its effect on the host's immune system.[85]

Since cyclosporine has been associated with cancer progression, the presence of preexisting malignancy may be a contraindication to its use. Patients with severely compromised renal function are also not candidates for cyclosporine therapy. It is a pregnancy category C drug and should be used with caution in pregnant women.

Methotrexate. The antimetabolite methotrexate is a folic acid analog. It inhibits dihydrofolate reductase, thus interfering with DNA and RNA synthesis. Low-dose therapy may be beneficial in chronic noninfectious ocular inflammatory disease in adults and children.[86–88] One disadvantage of this drug is the length of time it takes to achieve a therapeutic response. Side effects of methotrexate include hepatic fibrosis and cirrhosis, nausea, malaise, alopecia, and mouth ulcers.[86] It may also increase the risk of secondary malignancy. Pregnancy is an absolute contraindication because of the risk of abortion. Methotrexate is also contraindicated in breast-feeding women because of toxicity to the infant.

Azathioprine. Azathioprine is a derivative of 6-mercaptopurine that interferes with the synthesis of purine bases. It has been used alone and in combination with corticosteroids in the treatment of intraocular inflammation. There have been conflicting reports on its efficacy, but at least one controlled trial demonstrated that it was superior to placebo in patients with Behçet's disease.[89]

Azathioprine is generally used as a corticosteroid-sparing agent. Because an anti-inflammatory effect may not be evident for 3 to 4 weeks, the dosage of corticosteroids should be held constant until a therapeutic response is seen. Many patients require a concomitant low dose of prednisone.

Side effects are similar to those seen with methotrexate and include bone marrow suppression and hepatic damage. As with methotrexate, long-term use may increase the risk of malignancy, and after 6 months or 1 year of therapy, withdrawal of the drug is strongly encouraged. Patients with preexisting hepatic disease and those with active fungal, viral, protozoal, and bacterial infections should not be treated with azathioprine. Pregnancy is also a contraindication.

Cyclophosphamide (Cytoxan). Cyclophosphamide is an alkylating agent with inhibitory effects on both humoral and cellular immunity. It has a rapid onset of action and may be considered for use in cases of severe inflammation associated with Behçet's disease, necrotizing and nonnecrotizing scleritis, sympathetic ophthalmia, serpiginous choroiditis, and refractory intermediate uveitis.

Cyclophosphamide is a known bladder carcinogen, and its use may also result in other secondary malignancies. Other side effects include hemorrhagic cystitis (which may be a precursor to bladder malignancy), alopecia, anemia, leukopenia, thrombocytopenia, interstitial pulmonary fibrosis, gastrointestinal problems, and sterility. Cyclophosphamide may be teratogenic and should not be used in pregnancy (it is a pregnancy category D drug). Because it is excreted in breast milk, it is also contraindicated in lactating women.

The use of cyclophosphamide should be reserved for patients with sight-threatening disease who are poorly responsive to or intolerant of corticosteroids. It may also be used when an immediate effect is required, such as in patients with necrotizing scleritis in whom perforation is imminent. Its use is generally limited to a duration of 6 to 12 months, because the risk of secondary malignancy increases with increasing total dose.[90]

Chlorambucil (Leukeran). Chlorambucil is an alkylating agent that has a slower onset of action than cyclophosphamide. It is the result of a modification of mustard gas and, along with its active metabolite, disrupts DNA transcription and replication. The typical time to clinical response is approximately 3 weeks. It has been used to treat bilateral sight-threatening uveitides that are unresponsive or poorly responsive to corticosteroids, as well as to treat disease in patients who have become intolerant of corticosteroids. While it may be used as a corticosteroid-sparing agent, its usual use is as a replacement for corticosteroids.

Chlorambucil may be administered using a long-term, low-dose protocol, or it may be used in higher doses for shorter time periods. The low-dose, long-term regimen has been associated with significant risk of secondary malignancy, especially acute leukemia.[91,92] The high-dose, short-term protocol has, thus far, not been associated with the development of malignancy.[93,94] Other side effects of chlorambucil include bone marrow suppression, anorexia, nausea, weakness, emesis, and infertility.

Chlorambucil is teratogenic and should not be used in pregnant women (it is a pregnancy category D drug). Its use is also discouraged in breast-feeding patients, and it should not be used in patients with underlying neutropenia or thrombocytopenia.

Summary. The alkylating agents cyclophosphamide and chlorambucil may have an advantage over cyclosporine and methotrexate, because the alkylating agents often permit the discontinuation of corticosteroids. For example, patients with Behçet's disease and sympathetic ophthalmia may go into long-term remission after treatment with cyclophosphamide or chlorambucil, while inflammation may often recur with discontinuation of agents such as cyclosporine.[95–97] This advantage is counterbalanced by a more severe side effect profile, making these agents appropriate only in severe, sight-threatening disease.

New Immunosuppressive Agents

Mycophenolate Mofetil (Cellcept). Mycophenolate is an antimetabolite that inhibits purine metabolism. It is in the same family as azathioprine, but it may have lower toxicity and higher efficacy. It has been shown to inhibit the development of experimental autoimmune uveitis.[98] When used in combination with other agents, it can decrease the incidence of renal transplant rejection.[99] It has also been used to treat autoimmune and inflammatory skin diseases[100] and has recently been shown to be useful in suppressing inflammation in patients with severe uncontrolled ocular inflammatory disease.[101] It may be used as a corticosteroid-sparing agent and is also effective when used in combination with cyclosporine. While mycophenolate has not been extensively studied, it is a potentially useful agent in the treatment of sight-threatening uveitis.

The most frequent side effect of mycophenolate is diarrhea, and it may result in reversible villous atrophy.[102] It is known to be teratogenic in animals and should not be used in pregnancy.

Tacrolimus (Prograf, FK506). While tacrolimus has a very different structure than cyclosporine, its intracellular actions are very similar. It has been used to treat uveitis secondary to Behçet's disease, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, and idiopathic retinal vasculitis.[103–106] It is most effective early in the course of therapy, but its effectiveness may decrease gradually with prolonged treatment.

The main side effects of tacrolimus are renal impairment; central nervous system symptoms such as headache, tremor, dizziness, forgetfulness, and seizure; hyperglycemia; gastrointestinal symptoms; and electrolyte abnormalities.[107,108] Tacrolimus is category C and should be avoided during pregnancy, and nursing mothers should also not use it.

Future Horizons

Cytokines such as interleukin-2 (IL-2) and tumor necrosis factor (TNF) have been implicated in the pathogenesis of inflammatory disease. Selective blockade of these factors has therefore been suggested as a mechanism of modulating inflammation. A number of new cytokine inhibitors and immunomodulatory agents have recently been approved by the FDA for use in non-ophthalmic conditions, and they have potential for the treatment of uveitis. Controlled studies of these agents are needed in uveitis, but their use may be considered as a last resort in patients with potentially blinding disease that is refractory to other therapies.

Leflunomide (Arava). Leflunomide is an immunomodulatory agent that inhibits pyrimidine synthesis by means of a selective inhibition of dihydroorotate dehydrogenase. Activated T-cells are very susceptible, because they synthesize their pyrimidines primarily using this enzyme.[109] The drug also inhibits cytokine and growth factor receptor–associated tyrosine kinase activity. It was FDA-approved in September of 1998 for the treatment of rheumatoid arthritis but has

not yet been studied in uveitis. Leflunomide is contraindicated in pregnancy, because animal data have shown it to be teratogenic.

Dacluzimab (Zenapax). Dacluzimab is a humanized IL-2 receptor monoclonal antibody that is 90% human and 10% murine. It binds with the Tac subunit of the IL-2 receptor, thereby inhibiting IL-2 binding. Because the Tac subunit is expressed only on activated lymphocytes, it is these active cells that are the most susceptible.[110] Dacluzimab is administered intravenously at a usual dose of 1 mg per kg every 2 weeks. In clinical trials it was found to prevent primary renal transplant rejection,[111,112] and it was FDA-approved in 1998 for patients receiving kidney transplants. Humanized anti-Tac antibodies have been demonstrated to inhibit experimental autoimmune uveitis in a monkey model.[113] Dacluzimab has also been studied in a small series of patients with severe, chronic intermediate and posterior uveitis, and the majority of patients on this therapy were able to stop their standard immunosuppression. [114] No randomized clinical trials have been performed, but dacluzimab may hold promise for the treatment of autoimmune uveitis.

Etanercept (Enbrel). Etanercept is a TNF antagonist. It is a recombinant fusion protein made up of two soluble TNF receptors and the Fc portion of human IgG. Etanercept is a competitive inhibitor that binds and inactivates TNF. The drug is administered subcutaneously twice weekly and was approved by the FDA in 1998 for the treatment of rheumatoid arthritis. Etanercept is apparently well tolerated and is currently being investigated as a treatment for uveitis.

Infliximab (Remicade). Infliximab is a chimeric human-murine antibody to TNF that blocks receptor binding.[115] It was FDA-approved in 1998 for the treatment of Crohn's disease and is given intravenously over a 2-hour infusion. The majority of data involve single-dose regimens, although a number of studies have looked at multi-dose regimens. Infliximab is currently under investigation for rheumatoid arthritis, but it has not yet been studied in uveitis.

Surgical Management of Noninfectious Uveitis

Cataract is a frequent complication of uveitis. Once cataract develops in a uveitis patient, the management is more complex than in the non-uveitis patient. The presence of posterior synechiae, pupillary membranes, and inflammation may make the surgery more difficult and the postoperative course stormier. Ideally, control of inflammation should be obtained for at least 3 months before proceeding with surgery.[116] Preoperatively, the patient is often treated with topical corticosteroids, and oral corticosteroids may also be started a short time before surgery. The surgery itself may be complicated by difficulties with pupillary dilation. Synechiolysis and sphincterotomies may be required, and the use of iris hooks may greatly facilitate pupillary dilation.

The decision as to whether an intraocular lens should be implanted is still controversial. There is much evidence that an IOL may be safely implanted in cases of Fuchs iridocyclitis and pars planitis.[117–120] In contrast, the evidence in children with juvenile rheumatoid arthritis (JRA) is clearly in favor of

lensectomy with vitrectomy and no IOL placement.[121,122] More controversial is whether an IOL can safely be implanted in an adult eye with a history of JRA-associated uveitis. One uncontrolled series reported that IOLs may be safely implanted into selected patients with JRA.[123] However, the follow-up in this series was short, and there were only four adult patients in the series. It may be that intraocular lenses are a reasonable option for certain adult patients with quiet JRA but, as noted in the editorial regarding the above article, "additional clinical investigation in this area is warranted."[124] Patients with other causes of uveitis will often tolerate an intraocular lens but, again, the inflammation must be adequately controlled preoperatively.[125,126]

Polymethylmethacrylate (PMMA) IOLs are available that are coated with heparin. These heparin-surface-modified IOLs were designed in order to decrease the ability of inflammatory cells and debris to stick to the IOL. They appear to be well tolerated although they do not seem to offer much advantage over PMMA.[127–129] First-generation silicone foldable IOLs were associated with greater inflammatory response than PMMA when implanted into patients with uveitis; the newer silicone IOLs may be better tolerated.[130,131] Acrylic foldable lenses appear to be well tolerated in uveitis.

Posterior capsule opacification is a common complication after cataract surgery in uveitis patients. Occasionally, even an eye with little preoperative inflammation may form a membrane around an intraocular lens. The development of a membrane around the IOL has been reported to occur in the postoperative period even in the absence of significant anterior chamber reaction.[132] These cocoon-like membranes may be lysed with the Nd-YAG laser, but they tend to recur. It is therefore important to be vigilant in the early postoperative period, aggressively treating any signs of inflammatory deposits on the intraocular lens, even in the absence of significant anterior chamber inflammation. If Nd-YAG laser membranectomy is required, vigorous anti-inflammatory treatment should be undertaken to prevent reformation of the membrane. Rarely, removal of the IOL may be required. Pars plana vitrectomy may also be performed at the time of cataract surgery in uveitis patients when there is significant vitreous debris that would preclude good postoperative visual acuity.[133]

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