PERSPECTIVE

Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel

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• PURPOSE: To provide recommendations for the use of immunosuppressive drugs in the treatment of patients with ocular inflammatory disorders.

• PARTICIPANTS: A 12-person panel of physicians with expertise in ophthalmologic, pediatric, and rheumatologic disease, in research, and in the use of immunosuppressive drugs in patient care.

• EVIDENCE: Published clinical study results. Recommendations were rated according to the quality and strength of available evidence.

• PROCESS: The panel was convened in September of 1999 and met regularly through May 2000. Subgroups of the panel summarized and presented available information on specific topics to the full panel; recommendations and ratings were determined by group consensus.

• CONCLUSIONS: Although corticosteroids represent one of the mainstays in the management of patients with ocular inflammation, in many patients, the severity of the disease, the presence of corticosteroid side effects, or the requirement for doses of systemic corticosteroids highly likely to result in corticosteroid complications supports the rationale for immunosuppressive drugs (for example, antimetabolites, T-cell inhibitors, and alkylating agents) being used in the management of these patients. Because of the potential for side effects, treatment must be individualized and regular monitoring performed. With careful use of immunosuppressive drugs for treatment of ocular inflammatory disorders, many patients will benefit from them either with better control of the ocular inflammation or with a decrease in corticosteroid side effects. (Am J Ophthalmol 2000;130:492–513. © 2000 by Elsevier Science Inc. All rights reserved.)

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OCULAR INFLAMMATORY DISORDERS HAVE GREAT potential for visual morbidity and visual loss. In one large series of patients with uveitis, 35% had visual loss to a level of worse than 20/60 in at least one eye and 22% became unilaterally or bilaterally blind (worse than 20/200).[1] Cicatricial pemphigoid, if untreated, often results in blindness. Scleritis, particularly necrotizing scleritis, and necrotizing keratitis may threaten the structural integrity of the eye and may herald the onset of a potentially life-threatening systemic vasculitis. As such, the correct treatment of ocular inflammatory disorders is important for preserving vision and for preventing both ocular and nonocular morbidity.

Corticosteroids have been the mainstay of therapy for ocular inflammatory diseases since their development. Corticosteroids may be administered either topically, as

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TABLE 1. Levels of the Strength and Quality of Evidence-considered Categories of the Strength of a Recommendation

(A)	Strong evidence of efficacy and substantial clinical benefit support recommendation for use; should always be offered
(B)	Moderate evidence of efficacy or strong evidence of efficacy, but only limited clinical benefit supports recommendation for use; should generally be offered
(C)	Evidence of efficacy is insufficient to support a recommendation for or against use or evidence of efficacy may not outweigh adverse consequences, such as toxic effects, drug interactions, or cost of the chemoprophylaxis or alternative approaches; optional
(D)	Moderate evidence of lack of efficacy or of adverse outcome supports a recommendation against use; should generally not be offered
(E)	Good evidence of lack of efficacy or of adverse outcome supports a recommendation against use; should never be offered
(I)	Evidence from at least one properly randomized controlled trial
(II)	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, or from multiple time-series studies, or dramatic results from uncontrolled experiments
(III)	Evidence from opinions of the panel

Recommendations were rated according to the strength and quality of available evidence. The categories have been adapted from Gross and associates.[2]

periocular injections, or systemically (primarily orally but also by the intravenous or intramuscular route). Topical corticosteroids penetrate well only into the anterior segment of the eye and are useful in the management of anterior uveitis and episcleritis. Periocular corticosteroids are useful in the management of intermediate uveitis associated with decreased vision, the management of macular edema in association with panuveitis or posterior uveitis, and in selected other situations. The periocular route results in high local concentrations of corticosteroids in both the anterior and posterior segments of the eye typically without systemic side effects. However, either because of the nature of the disease or because of problems with the local (periocular) administration of corticosteroids (for example, corticosteroid-induced ocular hypertension) many patients will need systemically administered corticosteroids, typically oral prednisone. In patients with acute or episodic disease, a short course of oral corticosteroids may be useful for the suppression of the inflammation. In patients with chronic disease, initial treatment with high-dose oral prednisone, followed by tapering to low-dose oral prednisone, and long-term suppressive corticosteroid therapy may be necessary to control the inflammation.

However, in some patients systemic corticosteroids are insufficient to control the disease, and immunosuppressive drug therapy is required. In other patients, corticosteroid side effects result in the need for a corticosteroid-sparing agent, and in many patients the long-term use of systemic corticosteroids at the dose required to suppress the ocular inflammation is sufficiently likely to produce side effects that a corticosteroid-sparing agent is warranted. In these situations, immunosuppressive drugs have a role to play in the management of patients with ocular inflammatory disease.

A panel of physicians with expertise in clinical investigation, ophthalmology, rheumatology, pediatrics, and patient care in the field of inflammatory diseases was convened to review the role of immunosuppressive drugs in the management of ocular inflammation. The panel reviewed available data and developed recommendations for the use of these drugs. The recommendations were rated according to the strength and quality of the supporting evidence presented using a system similar to that developed by the US Public Health Service/Infectious Diseases Society of America (Table 1).[2] The goals of this report are to assist clinicians in determining when an immunosuppressive drug might be appropriate in the management of ocular inflammatory disease, to aid general ophthalmologists in the selection of patients for referral, and to provide guidelines for the use of these drugs.

ORAL CORTICOSTEROIDS

CORTICOSTEROIDS ARE USED WITH GREAT BENEFIT FOR inflammatory diseases of a noninfectiouscause. Corticosteroids are the initial drug for many autoimmune diseases, such as systemic lupus erythematosus, polymyositis, vasculitis, and sarcoidosis, and are effective in "flares" of rheumatoid arthritis, asthma, atopic dermatitis, and clinical subsets of other inflammatory and occasionally postinfectious diseases. This clinical utility is limited by side effects attendant to the chronic corticosteroid use, particularly in children who have not completed their growth. However, long-term studies of patients with sarcoid uveitis have shown that oral corticosteroid therapy is associated with substantially better visual outcomes, suggesting that systemic therapy has an important role to play in the management of patients with chronic uveitis.[3] Prednisone is the most commonly used oral corticosteroid, but for persons with serious liver dysfunction, prednisolone, the active form of prednisone, often is prescribed. The initial

TABLE 2. Suggested Guidelines for the Use of Prednisone for Chronic Ocular Inflammation

Parameter	Suggested Guideline
Initial dose	1 mg/kg/day*
Maximum adult oral dose	60–80 mg/day
Maintenance dose (adult)	≤10 mg/day
Tapering schedule	Over 40 mg/day, decrease by 10 mg/day every 1–2 weeks
	40–20 mg/day, decrease by 5 mg/day every 1–2 weeks
	20–10 mg/day, decrease by 2.5 mg/day every 1–2 weeks
	10–0 mg/day, decrease by 1 to 2.5 mg/day every 1–4 weeks
Monitor	Blood pressure, weight, glucose every 3 months
	Lipids (cholesterol and triglycerides) annually
	Bone density within first 3 months and annually thereafter
Supplemental treatment	Calcium 1500 mg daily and vitamin D 800 IU daily
	Estrogens and antiresorpative agents as needed

*In selected situations, where an immediate effect is needed, some investigators will begin with intravenous methylprednisolone at a dosage of 1 gm/day for 3 days and then start oral prednisone.

dose of prednisone typically is 1 mg per kg per day, for example, 60 to 80 mg per day in an adult. Methylprednisolone (Medrol; Pharmacia and Upjohn, Peapack, New Jersey) dose packs are not expected to be useful in chronic uveitis, because the corticosteroids are tapered too rapidly. For immediate control of vison-threatening diseases, methylprednisolone sodium succinate (Solu-Medrol; Pharmacia and Upjohn, Peapack, New Jersey) can be given intravenously over a period of more than 30 minutes. The usual regimen consists of 1 g pulses per day given on 3 consecutive days and is followed by oral corticosteroid therapy.[4]

Typically high-dose oral corticosteroids are continued for no longer than 1 month. If the patient's disease worsens on high-dose prednisone, or if there is no response after 2 to 4 weeks, an immunosuppressive agent should be added. Similarly, if the disease is not completely quiet after 4 weeks of high-dose oral prednisone, an immunosuppressive drug should be considered.

After a satisfactory anti-inflammatory response, the oral corticosteroids should be tapered and discontinued if possible. For patients with chronic disease on prednisone therapy, a representative tapering regimen is outlined in Table 2. If the inflammation exacerbates during the tapering schedule, resume a higher dosage for another month or until the disease is quiet and taper back to just above the threshold at which the disease reactivated. If chronic oral corticosteroid therapy is needed, some clinicians will convert the prednisone to an alternate day schedule, which may reduce toxicity but also may be less effective. If chronic suppression of disease requires much more than 10 mg per day of prednisone or its equivalent, an immunosuppressive drug should be considered. It is wise to caution the patient that the hypothalamic–pituitary axis may not return for 6 to 12 months after tapering of chronic oral corticosteroid therapy. Many patients wear a bracelet or carry a wallet card that alerts emergency personnel that the patient is taking or has taken exogenous corticosteroids and should receive a supplemental dose when injured or unconscious.

Some patients with acute ocular inflammation or with an acute flare of the ocular inflammation may benefit from a short course of oral corticosteroids. In this case, the duration of oral corticosteroid therapy typically is shortened to a total of 3 to 6 weeks. A representative approach would be to use an initial dose of 1 mg per kg per day for 1 week, and then taper using the same increments as outlined in Table 2 but decreasing them every 1 to 2 days, instead of every 1 to 2 weeks. Although the hypothalamic–pituitary axis may not be affected if the total duration of oral corticosteroid therapy is less than 3 weeks, too rapid tapering of the oral corticosteroid may result in a rebound of the ocular inflammation. Therefore, tapering is recommended. As each patient's ocular inflammation will vary in its response to treatment, treatment needs to be individualized.

• **ADVERSE EVENTS AND MONITORING:** The patient must be counseled about 1) the Cushingoid changes of facial and body appearance (moon facies, weight gain, fat redistribution, and increased acne) when prednisone is administered at larger than the physiologic doses of 5 to 10 mg per day and 2) the dangers of abrupt discontinuation of corticosteroids after the adrenal glands have been suppressed. Children below the age of 15 years are likely to experience delay of pubertal growth even with alternate day prednisone therapy.[5] Discussion should ensue about the need to monitor for infection, hypertension, fluid retention, diabetes mellitus, hyperlipidemia, atherosclerosis, osteoporosis, glaucoma, and cataracts. Other potential side effects include anxiety, sleeplessness, mood changes, easy bruising, and poor wound healing.

Blood pressure and blood glucose should be monitored every 3 months. Bone mineral density evaluations and

blood cholesterol and lipids should be monitored on an annual basis. Patients who are prescribed more than 7.5 mg per day and more than 30 mg per day of prednisone lose 10% to 15% and 30% to 50%, respectively, of the trabecular bone of the lumbar spine within 1 year.[6] Thus, most experts recommend 1500 mg of calcium and 800 IU of vitamin D daily, replacement of the sex hormones if decreased or if postmenopausal, and weight-bearing exercises for all who take chronic oral corticosteroids, particularly in the first 6 months of glucocorticoid therapy when the bone loss is the greatest.[7] Bone mineral density measurements should be performed on patients with anticipated duration of corticosteroids over 3 months at 3 months or less of therapy and annually thereafter. If bone mineral density studies show osteoporosis, antiresorptive agents such as calcitonin, alendronate, etidronate, or residronate are prescribed.[8]

Less common but more severe adverse reactions may require adding immunosuppressive drugs to facilitate more aggressive tapering of the oral corticosteroids. Pancreatitis, aseptic necrosis of bone, insulin-dependent diabetes mellitus, myopathy, and psychosis usually prompt the addition of immunosuppressive drugs to reduce the dose of prednisone. Daily doses of prednisone over 60 mg for the first month of therapy and over 20 mg for the first 6 months of therapy are associated with a 15% to 20% risk of aseptic necrosis of bone.[9,10] The incidence of ulcer disease is not increased by any substantial degree (if at all) in patients treated with oral corticosteroids, and the routine use of H_2 blockers for patients taking prednisone is unnecessary.[11,12] However, all nonsteroidal anti-inflammatory drugs are associated with an increased risk of gastric ulceration, and the concomitant use of oral corticosteroids and oral nonsteroidal anti-inflammatory drugs is associated with a fourfold rise in the occurrence of gastric ulceration. All patients on oral nonsteroidal anti-inflammatory drugs, and in particular those on concomitant oral corticosteroids, should be monitored for the occurrence of gastrointestinal symptoms, and such symptoms should be evaluated and treated appropriately. Rapid intravenous administration of methyl prednisolone has been reported to induce arrhythmia, cardiovascular collapse, myocardial infarction, and severe infection. It seems prudent to administer the glucocorticoid over a period of 30 minutes or longer. Finally, studies of patients with rheumatoid arthritis have suggested that long-term corticosteroid therapy (several years) may be associated with an increased mortality.[13]

• **SUMMARY:** Oral corticosteroids are an effective therapy for the control of acute and chronic inflammation attendant to autoimmune diseases. With long-term administration of these drugs, the adverse effects temper the overall effectiveness. As such, patients who require chronic oral corticosteroid therapy, especially at doses greater than 10 mg per day, may require immunosuppressive drug therapy.

IMMUNOSUPPRESSIVE DRUGS

IMMUNOSUPPRESSIVE DRUGS CAN CONVENIENTLY BE grouped as antimetabolites, T-cell inhibitors, and alkylating agents. The antimetabolites include azathioprine (Imuran; Faro, Bedminster, New Jersey), methotrexate (Rheumatrex; Lederle Laboratories, Wayne, New Jersey), and mycophenolate mofetil (Cellcept; Roche, Basel, Switzerland). The T-cell inhibitors include cyclosporine (Sandimmune and Neoral; Novartis, Basel, Switzerland and SangCya; Sangstat, Fremont, California), and tacrolimus (Prograf; Fujisawa, Osaka, Japan). The alkylating agents include cyclophosphamide (Cytoxan; Bristol-Myers/Squibb, New York, New York) and chlorambucil (Leukeran; Glaxo Wellcome, Middlesex, United Kingdom). These drugs are summarized in Table 3. Because most of these drugs take several weeks to have an effect, immunosuppressive drug regimens for initial therapy of ocular inflammation typically include high-dose oral corticosteroids as well. Once the disease is quiet, the corticosteroids are tapered either to a low level or, if possible, discontinued. If an immunosuppressive drug is added to an oral corticosteroid regimen for a patient with chronic disease and the ocular disease is quiet, then the immunosuppressive drug is added at the appropriate dose and tapering of oral corticosteroids begun 4 to 8 weeks later. If the disease is active despite corticosteroid therapy, then the patient is treated as one would for initial therapy with high-dose corticosteroids and the immunosuppressive drug. Oral corticosteroids typically are needed in these situations because of their immediate anti-inflammatory effect and the ability to suppress the inflammation while immunosuppressive drugs are having their slower onset of effect.

• **AZATHIOPRINE:** *Mechanism of Action.* Azathioprine is a purine nucleoside analog. It interferes with adenine and guanine ribonucleotides by suppression of inosinic acid synthesis, which in turn interferes with DNA replication and RNA transcription.[14] Immunologically, azathioprine decreases the numbers of peripheral T and B lymphocytes,[15] and reduces mixed lymphocyte reactivity, interleukin-2 synthesis and IgM production.[16]

Pharmacokinetics. Azathioprine is well absorbed orally and cleaved to 6-mercaptopurine, which is metabolized in cells to thioinosinic and thioguanylic acid by the action of hypoxanthine phosphoribosyltransferase. These metabolites affect ribonucleotide synthesis.[17] There is an up to fourfold individual variation in the rate of metabolism of azathioprine. Because the metabolism of azathioprine is dependent on xanthine oxidase, care must be taken when using it in combination with allopurinol, which inhibits this enzyme.

Nonophthalmic Uses. The most common use of azathioprine is in transplantation, especially in combination with

TABLE 3. Immunosuppressive Drugs for Ocular Inflammation

Class	Generic Name (Trade Name)	Oral Formulation	Initial Dose	Maximum Dose
Antimetabolite	Azathioprine (Imuran)	50-mg tablet	1 mg/kg/day	2.5–4 mg/kg/day
	Methotrexate (Rheumatrex)	2.5-mg tablet	7.5–12.5 mg/wk	25 mg/wk PO, SC, or IM
	Mycophenolate mofetil (Cellcept)	250-mg capsule 500-mg capsule 200-mg/ml oral suspension	500 mg BID	1.5 gm BID
	Leflunomide (Arava)	10-mg, 20-mg, 100-mg tablet	100 mg QD × 3, then 20 mg QD	20 mg QD
T-cell inhibitor	Cyclosporine (Sandimmune, Neoral, SangCyA)	Sandimmune 25-mg, 50-mg, 100-mg capsule, 100-mg/ml oral suspension; Neoral 25-mg, 100-mg capsule, 100-mg/ml oral suspension	2.5-5.0 mg/kg/day (divided dose)	10 mg/kg/day
	Tacrolimus (Prograf)	0.5-mg, 1-mg, 5-mg capsule 5-mg/ml oral suspension	0.15–0.30 mg/kg/day	0.30 mg/kg/day
Alkylating agent	Cyclophosphamide (Cytoxan)	25-mg, 50-mg tablet	2 mg/kg/day	3 mg/kg/day
	Chlorambucil (Leukeran)	2-mg tablet	0.1 mg/kg/day	0.2 mg/kg/day

Continued on next page

other agents such as prednisone and cyclosporine. Azathioprine also has been approved by the US Food and Drug Administration for use in rheumatoid arthritis. Placebo-controlled trials also have shown efficacy in psoriatic arthritis, Reiter syndrome, and systemic lupus erythematosus.[18,19]

Clinical Experience for Inflammatory Eye Disease. Uncontrolled case series of azathioprine suggested that it was effective for the treatment of chronic uveitis, usually in combination with corticosteroids.[20,21] In a placebo-controlled trial of 73 patients with Behçet disease, azathioprine was effective in decreasing the occurrence of eye

TABLE 3. *(Continued)* Immunosuppressive Drugs for Ocular Inflammation

Mechanism	Expected Onset	Lab Test*	Representative Side-effects†	Comments
Alters purine metabolism	1–3 months	CBC Q 4–6 weeks Chemistry Q 12 weeks	Bone marrow suppression (leukopenia thrombocytopenia), GI upset, hepatitis	Can be given once daily, or as divided dose twice daily.
Antimetabolite; inhibitor of dihydrofolate reductase	2 weeks to 3 months	CBC, LFTs Q 6–8 weeks	Bone marrow suppression (leukopenia thormbocytopenia), stomatitis, hair loss, nausea/vomiting, GI upset, hepatotoxicity (hepatitis, cirrhosis), pneumonitis, fetal loss	Folic acid 1 mg/day
IMP dehydrogenase inhibitor (purine synthesis)	2 weeks to 3 months	CBC, chemistries Q month	Diarrhea, nausea, neutropenia, infection	Possibly better tolerated than azathioprine, not well studied for uveitis
Dihydroorotate dehydrogenase inhibition (pyrimidine synthesis)	2 weeks	CBC Q 6 weeks, chemistry Q 12 weeks	Cytopenias, fetal loss, diarrhea, hypertension	Not studied in uveitis
T-cell inhibitor	2–6 weeks	Creatine Q month, CBC, LFTs, and Mg^{2+} Q 12 weeks	Renal dysfunction, tremor, hirsutism, hypertension, gum hyperplasia	Neoral has a greater bioavailability than Sandimmune. Follow BP
T-cell inhibitor		CBC, chemistry, and Mg^{2} Q month	Nephrotoxicity, HBP, neurotoxicity, hyperkalemia, hypomagnesemia, hepatitis, diabetes	Follow BP
Lymphotoxicity	2–8 weeks	CBC, UA Q 1–4 weeks	Bone marrow suppression, infection, hematuria and hemmorrhagic cystitis, increased risk malignancy, sterility, alopecia	May be given as IV pulse but not usually for uveitis
Lymphotoxicity	4–12 weeks	CBC Q 1–4 weeks	Bone marrow suppresson, infection, increased risk malignancy, sterility	

BID = twice daily; BP = blood pressure; CBC = complete blood count; D = day; GI = gastrointestinal; HBP = high blood pressure; IM = intramuscular; IV = intravenous; LFTs = liver function tests (primarily aspartate and alanine aminotransferases); PO = orally; Q = every; SC = subcutaneously; UA = urinalysis.

*Laboratory tests are obtained more frequently at the initiation of therapy; if the dose of the drug is changing, and if borderline toxicity or rapidly changing laboratory values are encountered.

†Space precludes listing all potential adverse effects.

disease in those without ocular involvement and decreasing the occurrence of second eye disease in those with unilateral disease.[22]

Dosage and Administration. Azathioprine is administered orally at a dose of 1 to 3 mg per kg per day. The most effective dose appears to be 2 mg per kg per day. The dose should be decreased when used with allopurinol. Dosing usually needs to be adjusted based on the clinical response and side effects.

Side Effects and Monitoring. The most common severe side effect of azathioprine is reversible bone marrow suppression, which is unusual when azathioprine is used in

the lower dosage range. Although an increased risk of malignant disease (especially non-Hodgkin lymphoma) has been reported in renal transplant patients treated with azathioprine, whether the risk is increased in patients with autoimmune diseases is unclear.[23] Other serious side effects include hepatoxicity, which occurs in less than 2%. The most common side effect is gastrointestinal intolerance, primarily manifested as gastrointestinal upset, nausea, and less commonly vomiting, which may be seen in up to 25% of patients and may result in discontinuation of therapy. When using azathioprine, a complete blood count and platelet count should be performed every 4 to 6 weeks. In addition, the liver function tests aspartate aminotransferase and alanine aminotransferase tests should be performed every 12 weeks. When toxicity occurs (liver function test greater than 1.5 times upper limit of normal), the dose should be decreased by 25 to 50 mg per day, and the liver enzyme level reevaluated after 2 weeks. If there is marked enzyme elevation (for example, greater than five times upper limit of normal), then azathioprine therapy should be discontinued, at least temporarily. Once liver enzymes return to normal, resume every 4 to 6–week and 12-week laboratory evaluations.

• **METHOTREXATE**: *Mechanism of Action*. Methotrexate is a folic acid analog and an inhibitor of dihydrofolate reductase, the enzyme responsible for the conversion of dihydrofolate to tetrahydrofolate. This action inhibits the production of thymidylate, which is essential for DNA replication.[24] As such, methotrexate inhibits rapidly dividing cells, such as leukocytes, producing an anti-inflammatory effect.

Pharmacokinetics. When given orally, up to 35% may be metabolized by the intestinal flora before absorption. The percentage of absorption decreases as the dose increases. When given parenterally, methotrexate is completely absorbed. Methotrexate is eliminated primarily through the kidney. The half life is approximately 3 to 10 hours, although at higher dosages the half life may be prolonged to 8 to 15 hours.

Nonophthalmic Uses. Methotrexate has been shown to be effective in the management of several systemic inflammatory diseases, including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus.[25] One advantage of methotrexate is the extensive experience with and the relative safety of its use in children with juvenile rheumatoid arthritis.[26] Methotrexate also is used as an antineoplastic agent at doses much higher than those used to treat systemic inflammatory conditions.

Clinical Experience for Inflammatory Eye Disease. Three small, uncontrolled, case series each of 11 to 22 patients have used methotrexate to treat various ocular inflammatory diseases, including vasculitis, panuveitis, intermediate uveitis, vitritis, scleritis, orbital pseudotumor, myositis, and sarcoid-associated panuveitis.[27–29] In general, preserved or improved visual acuity, decreased corticosteroid use, and decreased ocular inflammation were reported.

Dosage and Administration. Methotrexate typically is administered at a dose ranging from 7.5 to 25 mg once per week in a single undivided dose. The most common dose is 15 mg once weekly. Although many clinicians will initiate therapy at 7.5 mg per week and increase the dose to 15 mg per week over 1 to 4 weeks, others will start with higher doses. Although it is most often given orally, in some cases methotrexate's efficacy may be enhanced and its side effects minimized by intramuscular or subcutaneous injection. Typically, folate (1 mg per day) is administered concurrently with methotrexate to minimize nausea. The full effect from methotrexate therapy takes 6 to 8 weeks to occur.[28]

Side Effects and Monitoring. The most serious side effects of methotrexate are hepatoxicity, cytopenias, and interstitial pneumonia. Abnormal liver function tests occur in 15% of patients on methotrexate, but hepatic cirrhosis occurs in only 0.1%. The most common side effects are gastrointestinal and include stomach upset, nausea, stomatitis, and anorexia occurring in 5% to 25% of patients. Alopecia and rash occur less commonly. Methotrexate is a teratogen and is contraindicated in pregnancy. At the initiation of methotrexate therapy, a complete blood count, serum chemistry profile, hepatitis B surface antigen, and hepatitis C antibody are obtained. Complete blood count and liver function tests are obtained every 1 to 2 months. If the aspartate aminotransferase or alanine aminotransferase is more than two times normal on two separate occasions, the dose should be reduced. Liver biopsy is obtained if abnormalities in liver function tests persist after discontinuation of the drug.[30] Rarely cirrhosis may occur even in the absence of abnormal liver function tests. Because of potential hepatotoxicity, patients should be advised to abstain from alcohol consumption while receiving methotrexate therapy.

• **MYCOPHENOLATE MOFETIL**: *Mechanism of Action*. Mycophenolate mofetil is a selective inhibitor of inosine monophosphate dehydrogenase that interferes with guanosine nucleotide synthesis. Its major effects are on T and B lymphocytes. It prevents lymphocyte proliferation, suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium, and decreases recruitment of leukocytes to sites of inflammation.

Pharmacokinetics. The drug has high oral bioavailability but should be ingested on an empty stomach. It is metab-

olized to the active compound mycophenolic acid, which is excreted renally.

Nonophthalmic Uses. Mycophenolate mofetil has been used in the prevention of allograft rejection in cases of renal and cardiac transplantation. The addition of mycophenolate mofetil to oral corticosteroids and cyclosporine significantly reduces the occurrence of graft rejection.[31] When compared in randomized trials to azathioprine, and used in combination with oral corticosteroids and cyclosporine, mycophenolate mofetil was associated with a reduced rate of early graft failure, but significant long-term differences in efficacy could not be detected.[32] In transplant situations, it may be less well tolerated than azathioprine, with higher rates of viral infections and diarrhea[32]; however, it has been the experience of some panel members that it may be better tolerated than azathioprine by patients being treated for rheumatological disorders.

Clinical Experience for Inflammatory Eye Disease. Published experience on the use of mycophenolate mofetil for ocular inflammatory disease is limited. Two uncontrolled case series, totaling 26 patients, have reported that mycophenolate mofetil is an effective agent in the treatment of ocular inflammatory diseases.[33,34] Mycophenolate mofetil often was used in combination with other agents, particularly oral corticosteroids, and in some cases cyclosporine. A variety of ocular inflammatory disorders were treated, including uveitis and scleritis. Success typically was measured by the ability to control the inflammation and reduce the dose of corticosteroids and/or cyclosporine. It was the clinical impression of both groups of investigators that mycophenolate mofetil was effective for control of ocular inflammatory disease, when used in combination with other agents. Its efficacy relative to other immunosuppressive drugs for treatment of ocular inflammatory disease cannot be determined from published reports. It may be an acceptable alternative to azathioprine or methotrexate, especially in patients intolerant of other agents.

Dosage and Administration. Mycophenolate mofetil is generally used at an oral dose of 1 g twice daily. A dose of 3 g daily appears to have increased toxicity, whereas doses less than 2 g daily are believed to be less effective. Mycophenolate mofetil should be used with caution in patients with renal impairment and in those with gastrointestinal disorders, which might affect absorption.

Adverse Events and Monitoring.. Gastrointestinal problems (pain, nausea, vomiting, and diarrhea; up to 31%) were common side effects of mycophenolate mofetil in patients receiving the drug for prevention of allograft rejection.[31,32] Other reported complications in transplant patients receiving 3 g daily included leukopenia (up to 19%); lymphoma (1%); nonmelanoma skin cancers (9%); and opportunistic infections (up to 46%, the majority being cytomegalovirus and herpes simplex infections, with less than 2% being fatal). It should be remembered that these patients are also receiving other immunosuppressive drugs in combination with mycophenolate mofetil.

Larkin and Lightman[33] reported that only one of 11 patients treated with mycophenolate mofetil for ocular disease developed an adverse event, which consisted of nausea and headache, symptoms that did not recur when treatment was reinstituted at a dose 500 mg twice daily. Kilmartin and associates[34] reported that six of nine patients treated with mycophenolate mofetil at a dose of 1 g twice daily developed mild adverse reactions, including myalgia, fatigue, headache, and nausea.

Patients should be monitored with complete blood counts on a weekly basis for 4 weeks, then on a twice monthly basis for 2 months, with monthly testing thereafter. Members of the panel also monitor liver function tests every 3 months.

• **CYCLOSPORINE:** *Mechanism of Action.* A natural product of fungi, including *Beauveria nivea*, cyclosporine (cyclosporine A) is an 11-amino acid cyclic peptide. Cyclosporine appears to affect preferentially immunocompetent T lymphocytes that are in the G0 and G1 phase of their cell cycle, and its effect appears to be a specific transcriptional inhibition in these cells, blocking replication, as well as their ability to produce lymphokines, such as interleukin-2.[35]

Pharmacokinetics. Absorption of cyclosporine through the gut varies widely. Two oral preparations of cyclosporine, one a microemulsion (Neoral) and the other gelatin capsules (Sandimmune)[9] are available. The microemulsion preparation has greater bioavailability than the gelatin preparation; the two are not bioequivalent and cannot be used interchangeably. The drug is metabolized in the liver and excreted in the bile, with very little of the parent drug or its metabolites appearing in the urine. It is estimated that the terminal half-life of cyclosporine in the blood is approximately 8 hours, with a range of 5 to 18 hours. Within the vasculature, the drug distribution at steady state is approximately 35% to 45% in plasma and 40% to 55% within erythrocytes. Some 90% of the plasma portion of the drug is bound, mostly to lipoproteins. Cyclosporine leaves the vasculature readily and has been found in the intraocular fluids of uveitis patients.[35]

Nonophthalmic Uses. In the United States, cyclosporine is approved by the US Food and Drug Administration for the prevention and treatment of graft rejection, the treatment of severe, active rheumatoid arthritis that is poorly responsive to methotrexate, and for the treatment of severe, recalcitrant, plaque psoriasis in adults.[36]

Clinical Experience for Inflammatory Eye Disease. Uncontrolled case series suggested that cyclosporine was effective

for a variety of uveitis conditions as sole therapy at a dose of 10 mg per kg per day,[37] a dose that is higher than that currently used. In a randomized, controlled clinical trial of 56 patients with uveitis, cyclosporine was found to be similar to oral corticosteroids in terms of efficacy.[38] The authors noted enhanced efficacy of the two agents together. An uncontrolled, retrospective study of 15 children and adolescents with uveitis treated with cyclosporine reported that 82% of those patients had an improvement in their clinical disease, and that the drug was well tolerated.[39] A randomized controlled trial in Japan demonstrated that cyclosporine at a starting dose of 10 mg per kg per day was superior to colchicine in the treatment of the ocular complications of Behçet disease.[40] A good response was seen in approximately 50% of the patients treated with cyclosporine.

Dosage and Administration. For ocular disease, cyclosporine usually is given at a dose of 2 to 5 mg per kg per day, administered in an equally divided twice daily doses. Some clinicians will begin cyclosporine therapy with the microemulsion preparation (Neoral) at 2 mg per kg twice daily or with the gelatin capsules (Sandimmune) at 2.5 mg per kg twice daily and adjust the dose based on response and side effects.

Adverse Events and Monitoring. The most worrisome side effect of cyclosporine is nephrotoxicity. At the 10 mg per kg per day dose, all patients developed some evidence of nephrotoxicity.[41] At the currently used doses (2 to 5 mg per kg per day) the probability of nephrotoxicity appears to be reduced substantially. The other commonly encountered side effect is hypertension. Less commonly encountered side effects include hepatotoxicity, gingival hyperplasia, myalgias, tremor, paresthesiae, hypomagnesemia, and hirsutism. The patient's blood pressure should be checked at every visit and no less frequently than monthly initially and every 3 months for patients on long-term therapy. Serum creatinine should be checked every 2 weeks initially and monthly once dosage has stabilized. Serum concentrations of the drug may be used to monitor serum absorption, but do not correlate well with efficacy for autoimmune disorders, and are not needed routinely.

• **TACROLIMUS**: *Mechanism of Action*. Tacrolimus is a macrolide antibiotic produced by *Streptomyces tsukubaensis*. Tacrolimus inhibits the activation of T lymphocytes by a mechanism similar to that of cyclosporine.[42]

Pharmacokinetics. Absorption of tacrolimus from the gastrointestinal tract is both incomplete and variable. The plasma protein binding of tacrolimus is approximately 99%. Tacrolimus primarily is metabolized by the cytochrome p-450 system; fecal elimination accounts for over 90% of the elimination. In healthy research subjects, the half-life of orally administered tacrolimus was 34.8 ± 11.4 hours. Rate and extent of oral absorption of the drug are limited when the drug is taken with food.

Nonophthalmic Uses. Tacrolimus is used for prevention and treatment of solid organ transplant rejection. Randomized controlled clinical trials of liver transplant recipients showed lower rates of rejection in patients treated with tacrolimus when compared with cyclosporine-treated patients.[43,44]

Clinical Experience for Inflammatory Eye Disease. Small, uncontrolled case series have suggested that tacrolimus might be effective for the treatment of noninfectious uveitis. Success rates were on the order of 62% to 76% for control of the intraocular inflammation.[45–48]

Dosage and Administration. Tacrolimus is available for both intravenous and oral administration, but most patients with uveitis have been treated with oral tacrolimus. An initial oral dose of 0.10 to 0.15 mg per kg per day is recommended for adult patients who have had liver transplants. An initial dosage of 0.05 mg per kg per day may be effective for uveitis. Monitoring of blood concentrations may be necessary, as absorption varies.

Adverse Events and Monitoring. Major side effects include renal impairment (28%), neurologic symptoms (21%), gastrointestinal symptoms (19%), and hyperglycemia (13%).[45] Adverse effects resolve or improve when tacrolimus is stopped or when the dosage is reduced. Other reported adverse events include hypomagnesemia, tremor, headache, trouble sleeping, paresthesias, and hypertension. Tacrolimus should not be given with cyclosporine because of the similar risks of renal toxicity. Patients should be monitored closely for the occurrence of adverse events. Patients should undergo weekly laboratory assessment of the following: liver enzymes; bilirubin; blood urea nitrogen; creatinine; electrolytes including calcium, magnesium, and phosphate; cholesterol and triglycerides; glucose; and complete blood counts, at least initially. With stable dosing the frequency may be reduced to monthly. Blood pressure should also be monitored at every visit, at least monthly initially, and subsequently at least every 3 months.

• **CYCLOPHOSPHAMIDE**: *Mechanisms of Action*. Cyclophosphamide is a nitrogen mustard-alkylating agent the active metabolites of which alkylate purines in DNA and RNA, resulting in cross-linking, aberrant base pairing, ring cleavage and depurination.[49] This process results in cell death, because the cells are unable to replicate. Cyclophosphamide is cytotoxic to both resting and dividing lymphocytes. In patients, it decreases the number of activated T lymphocytes, suppresses helper T lymphocyte functions, and decreases B lymphocytes for months.[50] Cyclophosph-

amide suppresses both primary and established cellular and humoral immune responses, including delayed-type hypersensitivity, mixed lymphocyte reactions, mitogen-induced and antigen-induced blastogenesis, and production of cytokines.

Pharmacokinetics. Cyclophosphamide is well absorbed and is enzymatically converted by the hepatic microsomal enzymes to multiple metabolites, of which phosphoramide mustard is thought to be the most active.[51] It is extensively metabolized before excretion, primarily by the kidney, with less than 25% remaining unchanged in the urine.[51,52] One of these metabolites, acrolein, is thought to be responsible for the urologic toxicity.[53] The use of 2-mercaptoethane sulfonate may detoxify acrolein and reduce bladder toxicity. Both allopurinol and cimetidine inhibit hepatic microsomal enzymes, increasing the metabolites of cyclophosphamide.[51] Doses should be reduced 30% to 50% for renal failure.

Nonophthalmic Uses. The most common use of cyclophosphamide is in oncology as an antineoplastic agent, for which it is approved by the US Food and Drug Administration. It is used in several autoimmune diseases, the most common being systemic lupus erythematosus and vasculitis, particularly Wegener granulomatosis.[54–59] It also has been used for rheumatoid arthritis, primarily in patients with the secondary complication of vasculitis. Although there are placebo-controlled trials in both systemic lupus erythematosus and rheumatoid arthritis, there are none in vasculitis. Cyclophosphamide appears to be most beneficial when used on a daily oral basis,[59] although monthly intravenous administration is effective for lupus nephritis.

Clinical Experience for Inflammatory Eye Disease. The majority of the studies of cyclophosphamide for ocular diseases have been uncontrolled case series.[60–63] Intravenous pulsed cyclophosphamide appears to be less effective than oral daily cyclophosphamide and not particularly effective for uveitis.[61,62] In a small randomized, controlled, clinical trial, cyclophosphamide and corticosteroids were more effective than corticosteroids alone for mucous membrane pemphigoid with ocular involvement, both in terms of initial control of the disease and the ability to successfully taper the corticosteroids.[64]

Dosage and Administration. Orally, cyclophosphamide is given at 1 to 3 mg per kg per day. Many clinicians begin therapy at 2 mg per kg per day and adjust the dose depending on response and toxicity. The daily dosage typically is decreased by 25 to 50 mg for toxicity.

Adverse Events and Monitoring. The most common type of side effect seen with cyclophosphamide is bone marrow suppression, which is dose dependent, reversible, and more common in older individuals (older than 65 years).[40] Some investigators strive to lower the white blood count to a level of 3000 to 4000 cells per μl to induce a therapeutic effect. Substantial granulocytopenia to an absolute neutrophil count below 1000 cells per μl is associated with an increased risk of bacterial infections, in particular sepsis. Therefore, most clinicians will discontinue alkylating agents at a white count of 2500 cells per μl or below to avoid this complication. Rarely, myelodysplasia can be seen with long-term oral therapy. The second serious complication seen is hemorrhagic cystitis, which is uncommon and seen primarily in individuals with bladder stasis or those unable to take adequate fluids. Initially, this toxicity manifests as microscopic hematuria, but it can develop into gross hematuria and hemorrhagic cystitis. All patients on cyclophosphamide therapy should be encouraged to drink two or more liters of fluid per day to maintain a good urine flow and minimize toxicity. Bladder toxicity from cyclophosphamide requires discontinuation of cyclophosphamide. For patients who have a potentially fatal disease, such as Wegener granulomatosis, investigation of the bladder wall by cystoscopy followed by consideration of reinstitution of cyclophosphamide after resolution of the toxicity may be tried. Intermittent intravenous "pulse" cyclophosphamide with concomitant 2-mercaptoethane sulfonate therapy is one approach to avoid bladder toxicity. Conversely, for eye disease, some clinicians will discontinue cyclophosphamide with the occurrence of bladder toxicity and switch to an alternative approach. Chlorambucil, because it does not cause bladder toxicity, may be substituted for cyclophosphamide in this situation.

Other toxicities include teratogenicity (cyclophosphamide is contraindicated in pregnancy), ovarian suppression, testicular atrophy, and azospermia. Ovarian failure is age related with younger individuals being less affected (women under age 25 years have less than a 30% chance of ovarian failure as compared with greater than 50% over the age of 30 years). For patients beginning cyclophosphamide therapy, cryopreservation of eggs or sperm may be considered. Concomitant use of a gonadotropin-releasing hormone agonist also may prevent sterility in women receiving cyclophosphamide.[65–67] Less severe adverse events include alopecia, nausea, and vomiting. Alopecia occurs in up to 50% of individuals receiving cyclophosphamide. However, after therapy is complete, hair growth returns. Nausea and vomiting can be decreased with antiemetics and, to some degree, by adequate hydration.

In addition to granulocytopenia, lymphopenia is induced. Associated with lymphopenia is the possibility of opportunistic infections. In one randomized, controlled clinical trial of 50 patients, comparing intermittent intravenous "pulse" to oral daily cyclophosphamide for the treatment of Wegener granulomatosis, 70% of the patients treated with oral daily cyclophosphamide developed infections, including 30% who developed *Pneumocystis carinii* pneumonia.[50] Although there appears to be regional variations in the frequency in *P. carinii* pneumonia in immu-

nosuppressed patients, some clinicians advocate the initiation of *P. carinii* pneumonia prophylaxis (for example, trimethoprim/sulfamethoxazole one tablet orally daily or one double-strength tablet three times per week) with the initiation of treatment with alkylating agents.

For oral therapy, a complete blood count, platelet count, and urinalysis should be obtained weekly initially and, when dosing is stable, at least every 4 weeks. If mild bone marrow suppression is seen, the dosage should be lowered by 25 to 50 mg per day and the laboratory tests repeated in 2 weeks. If more severe bone marrow suppression is seen (for example, leukocytes less than 2500 cells per ml), therapy is interrupted until the counts have recovered, and then therapy is resumed at a lower dose. If hematuria (any level above standard normals for the laboratory) occurs, cyclophosphamide should be discontinued. If hematuria persists after 3 to 4 weeks, a urologist should be consulted.

• **CHLORAMBUCIL**: *Mechanism of Action*. Chlorambucil is an alkylating agent, which substitutes an alkyl group for hydrogen ions in organic compounds. DNA to DNA intrastrand crosslinking and DNA to protein crosslinking occur, which lead to interference in DNA replication, DNA transcription, and nucleic acid function. Chlorambucil has a relatively slow onset of activity.[68]

Pharmacokinetics. Oral bioavailability ranges from 56% to 100%. Food increases bioavailability. Plasma concentrations are reached in 1 hour. Metabolism to an active metabolite phenylacetic acid mustard occurs in the liver. Chlorambucil and phenylacetic acid mustard undergo hydrolysis to inactive compounds that are eliminated in the urine. The half-life of chlorambucil is 92 minutes, and the half-life of phenylacetic acid mustard is 145 minutes.

Nonophthalmic Uses. Chlorambucil is used to treat several oncologic malignancies, including leukemia, non-Hodgkin lymphoma, Hodgkin disease, and ovarian carcinoma. It has been used in rheumatic diseases, but less frequently than cyclophosphamide.[69] The one exception is Behçet disease, where there appears to be greater published experience with chlorambucil.[70–74]

Clinical Experience for Inflammatory Eye Disease. Small, uncontrolled case series suggest that chlorambucil may be effective for a variety of sight-threatening uveitic syndromes, including Behçet disease and sympathetic ophthalmia.[70–74] Some studies suggest that long-term drug-free remissions can be obtained after 6 to 24 months of therapy. Patients typically require concomitant oral corticosteroids initially, and one goal of chlorambucil therapy is to taper and discontinue oral corticosteroids over a 2-month to 4-month period.

Dosage and Administration. There are two approaches to the use of chlorambucil in patients with uveitis. The more traditional therapy consists of a dose of 0.1 to 0.2 mg per kg per day (6 to 12 mg daily) as a single daily dose. Therapy is given for 1 year after quiescence of the disease in an effort to induce a long-term drug-free remission.[70,71] Once the eye is quiet, oral corticosteroids are tapered and discontinued. Short-term, high-dose therapy consists of an initial dose of 2 mg daily for 1 week, followed by escalation by 2 mg per day each week. The dose escalation is continued until the inflammation is completely suppressed or until the white blood count decreases below 2400 cells per μl or the platelet count decreases below 100,000 cells per μl. If bone marrow toxicity is encountered, chlorambucil is discontinued. The typical duration of short-term, high-dose therapy is 3 to 6 months.[74]

Adverse Effects and Monitoring. The primary side effect of chlorambucil is bone marrow suppression. Typically this suppression is reversible, but it may be prolonged. Rarely, irreversible bone marrow aplasia may occur. Opportunistic infections, particularly viral infections such as herpes zoster, may occur while a patient is on chlorambucil therapy. As with the other alkylating agent, cyclophosphamide, prophylaxis for *P. carinii* pneumonia should be considered. Nausea is uncommon, and unlike cyclophosphamide, alopecia and bladder toxicity do not occur. Permanent sterility usually will occur in men on chlorambucil, and in women amenorrhea occurs.[75] Younger women may have return of menses and fertility, but in older women early onset menopause is typical. Chlorambucil is teratogenic and is contraindicated in pregnancy.

A complete blood count should be monitored on all patients receiving chlorambucil therapy. Initially the count should be performed weekly. Once a stable dose has been achieved, the frequency of monitoring may be reduced to monthly. For patients on short-term, high-dose chlorambucil, weekly monitoring is required throughout, as the dose is being escalated. Some clinicians believe that chlorambucil is more likely to induce thrombocytopenia than is cyclophosphamide.

• **ALKYLATING AGENTS AND MALIGNANCY**: The most worrisome potential side effect of treatment with alkylating agents is an increased risk of malignancy. Although there are concerns about increased rates of malignancy with all forms of immunosuppression, the data suggest that with other immunosuppressive drugs the rates may not be increased substantially in patients with autoimmune diseases.[76] However, in a randomized, controlled, clinical trial of 431 patients with polycythemia vera, the rate of acute leukemia was 13.5-fold greater with chlorambucil treatment than with phlebotomy or radioactive phosphorous.[77] Furthermore, the increase in malignancy appeared to be dose related. The rate was over fourfold greater for an average daily dose of over 4 mg. In a case-controlled study of 238 patients with rheumatoid arthritis, cyclophosphamide was associated with a 1.5-fold increase in the risk of

malignancy.[77] These malignancies included bladder cancer, skin cancer, and myeloproliferative malignancies. In this study, the rate of cancer was associated with a longer duration of treatment. Furthermore, the Kaplan-Meier curves for the occurrence of cancer did not begin to diverge until after 5 years of follow-up, suggesting that the effect is a long-term one.[78]

Most of the underlying disorders in which an increased risk of malignancy has been associated with alkylating agent therapy have been those with an intrinsic increased risk of malignancy. Therefore, the argument has been advanced that eye conditions, which may not be associated with an increased risk of malignancy on their own, may not be associated with a substantial increased risk of malignancy when treated with alkylating agents.[79] In a retrospective analysis of 543 patients with eye disease, 330 of whom were treated with immunosuppressive drugs, including 126 patients treated with alkylating agents, there was no excess risk of malignancy among those patients treated with immunosuppressive drugs.[79] However, in this study, because of issues related to study power (drugs with different malignancy risk were analyzed as a single group) and duration of follow-up (mean follow-up was approximately 3 years, which may have been too short to detect an increased risk of malignancy), an increased risk may have been missed. In this regard, the experience of the National Institutes of Health with use of cyclophosphamide for Wegener granulomatosis is instructive. Early studies published in 1973, 1974, and 1983 all suggested no increased risk of malignancies among patients treated with cyclophosphamide for Wegener granulomatosis. However, in a series published in 1992, with 158 patients followed for up to 24 years, there was a 2.4-fold increased risk of cancer compared with the expected rate and a 33-fold increased risk of bladder cancer.[58] Although the manner in which alkylating agents are used for ophthalmic disease (less than 18 months' duration of therapy) may decrease the probability of inducing malignancies, it would seem prudent to advise any patient being treated with chlorambucil or cyclosphosphamide of the potential for an increased risk of malignancy. Furthermore, because of the suggestion that hemorrhagic cystitis is a risk factor for subsequent bladder cancer in patients treated with cyclophosphamide, some clinicians would discontinue cyclophosphamide after the onset of hematuria to minimize any increased risk of bladder cancer.

• **SUMMARY:** All of the agents above appear to have efficacy in the treatment of ocular inflammation. Cyclosporine[40] and azathioprine[22] have been demonstrated to be effective in randomized, controlled clinical trials for the treatment of ocular inflammatory diseases (I; see Table 1). Methotrexate, mycophenolate mofetil, tacrolimus, cyclophosphamide, and chlorambucil all appear to have efficacy in uncontrolled case series (II), and cyclosphosphamide has been shown to be effective for the treatment of ocular involvement in mucous membrane pemphigoid in a randomized, controlled clinical trial (I).[64] Long-term treatment of the ocular inflammation may be needed with antimetabolites and T-cell inhibitors, whereas treatment with alkylating agents may result in long-term drug-free remissions (III).

Once a patient has been started on an immunosuppressive drug, and an effective drug and dose found, it typically is continued for 6 to 24 months. At that time attempts may be made to taper the medication over a period of 3 to 12 months. Tapering typically occurs at monthly to 6-week intervals because of the duration of effect of these drugs. However, some patients may need long-term or even indefinite treatment. Relative efficacy among the different agents has not been determined, and individual variation in response exists. As such, treatment should be individualized based on the patient's desires (for example, pregnancy) and other medical considerations.

• **COMBINATION THERAPY:** The therapeutic strategy to combine medications is employed frequently in the treatment of cancer. The immune system also lends itself to a multipronged attack, because a medication that preferentially affects one arm of the immune system (for example, antigen presenting cells, T lymphocytes, B lymphocytes, specific cytokines, or cell adhesion molecules on endothelial cells) could be effectively combined with a medication that targets a different arm. The hope is that such a combination would lead to enhanced immunosuppression without encountering dose-limiting toxicity.

Examples from Rheumatic Diseases. The strategy of combined therapy has been effectively employed in the treatment of rheumatic diseases. Examples include the use of hydroxychloroquine, sulfasalazine, and methotrexate to treat rheumatoid arthritis[80]; the combination of cyclosporine and methotrexate to treat rheumatoid arthritis[81]; or the use of tumor necrosis factor inhibition in combination with methotrexate to treat rheumatoid arthritis.[82] In each of these examples, randomized, controlled clinical trials have established the superiority of the combined therapy over the use of a single agent (monotherapy). In addition, corticosteroids routinely are added to various regimens for immunosuppression, such as in the therapy of polyarteritis nodosa, Wegener granulomatosis, or lupus nephritis with cyclosphosphamide. Most patients who undergo vital organ transplantation receive a combined immunosuppression regimen, such as azathioprine and cyclosporine.

Clinical Experience for Inflammatory Eye Disease. No randomized, controlled, clinical studies exist to evaluate the role of combined immunosuppressive therapy for inflammatory eye disease. Most practitioners who prescribe a medication such as cyclosporine, methotrexate, azathioprine, or cyclophosphamide also will prescribe a course of oral corticosteroids, at least initially. Corticosteroids en-

hance the immunosuppressive and anti-inflammatory effects of almost any modality of immunosuppression. One uncontrolled case series for the treatment of uveitis reported substantial benefit by combining methotrexate with cyclosporine and a corticosteroid.[83] Five eyes of three patients with serpiginous choroidopathy treated with the combination of azathioprine, cyclosporine, and corticosteroids have been reported with encouraging clinical responses.[84] The combination of an antimetabolite (for example, azathioprine, methotrexate, or mycophenolate mofetil) with cyclosporine is appealing, because the drugs have different toxicities and are frequently employed together in other situations, such as transplantation. Although alkylating agents are frequently combined with corticosteroids, they typically are not combined with other immunosuppressive drugs because of concerns about toxicity (for example, bone marrow suppression) and the degree of immunosuppression and the occurrence of infection.

Dosage and Administration. In general dosage should never exceed that given for individual medications, and the dosage may be reduced when combinations are employed. One goal of combination regimens is to minimize corticosteroid dosage.

Adverse Events and Monitoring. Office visits and laboratory testing should correspond to what is indicated for each individual medication in the combination. Monitoring, if anything, should become more vigilant when combinations are employed, because the number of potential complications and interactions increases with combinations. One major drawback to combination therapy is the increasing complexity of the regimens and the attendant problems with compliance.

SPECIFIC DISEASES

NEARLY ANY OCULAR INFLAMMATORY DISORDER REQUIRing chronic systemic corticosteroid treatment may require immunosuppressive drugs in an effort to reduce the dose of corticosteroids. The probability of using an immunosuppressive drug will vary depending on the severity of the underlying disease. For example, published series have suggested that 15% of patients with pars planitis will need immunosuppression,[85] but that 69% of patients with sympathetic ophthalmia will.[86] However, selected diseases, because of their poor natural history, are candidates for immunosuppressive drug therapy from the onset. These diseases include Behçet disease with posterior segment involvement and mucous membrane pemphigoid with ocular involvement. Other diseases, such as scleritis with systemic necrotizing vasculitis, require immunosuppressive drugs for treatment of the underlying disorder. Finally, some forms of posterior uveitis, such as serpiginous choroidopathy, appear to benefit from immunosuppressive drug therapy, but the disease is sufficiently uncommon that recommendations are less certain. Because of the effect of immunosuppressive drugs on the immune system, and because of their potential for side effects, accurate diagnosis of the ocular inflammatory disorder, particularly the exclusion of infection or malignancy, before the institution of such therapy is important.

• **BEHÇET DISEASE:** *Clinical Features.* The classic triad of Behçet disease is oral ulcers, genital ulcers, and uveitis. Oral ulcers are the most common manifestation and are present in 98% to 100% of cases, whereas ocular disease occurs in 68% to 100% of patients. Other manifestations include cutaneous lesions, such as erythema nodosum and superficial migratory thrombophlebitis, arthritis, vascular disease, including thrombotic lesions, and central nervous system disease.[87–90]

Anterior uveitis with or without a hypopyon is present in the majority of patients with ocular involvement from Behçet disease.[88] The more devastating ocular complication is posterior segment involvement, including vitritis, retinal vasculitis, focal necrotizing retinitis, and posterior uveitis,[88–91] which is associated with a poor visual outcome if untreated. Natural history studies show that 73% of patients with ocular Behçet disease develop blindness and that among those who develop no light perception vision, the average time to do so was 3.5 years.[91] Furthermore, it appeared that systemic corticosteroid therapy delayed the time to blindness but did not alter the long-term outcome.[91] As such, the occurrence of posterior uveitis in patients with Behçet disease usually is considered an indication for immunosuppressive drug therapy.

Clinical Experience with Immunosuppressive Drugs. Early experience in the use of immunosuppressive drugs for the treatment of Behçet disease was with chlorambucil. These reports typically consisted of uncontrolled, case series demonstrating an arrest of disease in patients treated with chlorambucil, followed by drug-free long-term remissions after 2 years of therapy.[72–74] No randomized controlled trials were done, but this experience compared favorably with the natural history and suggested that chlorambucil was effective in the treatment of patients with ocular Behçet. Although there are few published data using cyclosphosphamide for the treatment of ocular Behçet disease,[92] some clinicians consider it equally effective and easier to use than chlorambucil and will use cyclophosphamide rather than chlorambucil in this situation.

Cyclosporine has been used extensively for treatment of uveitis in patients with Behçet disease. A randomized, double-masked, controlled clinical trial of 96 patients demonstrated that cyclosporine was significantly better than colchicine for ocular Behçet disease.[40] Nearly 50% of patients treated with cyclosporine had a good response (75% to 100% reduction) for the frequency of ocular

attacks and a good response for the severity of ocular attacks. However, nearly 25% of the cyclosporine-treated patients had a slight reduction, no change, or worsening of the frequency of ocular attacks, and 33% had a slight reduction, no change, or worsening of the severity of ocular attacks. These data suggest that cyclosporine may not be beneficial for all patients with ocular Behçet disease. Furthermore, this study used a higher dose of cyclosporine (10 mg per kg per day) than is recommended currently (5 mg per kg per day).

A randomized, controlled, clinical trial of 73 patients compared azathioprine therapy, at a dose of 2.5 mg per kg per day, with placebo and showed that azathioprine was effective in preventing eye disease among those without eye disease at randomization and was effective in decreasing contralateral eye involvement among those with unilateral disease. Azathioprine was not completely effective, because 22% of the patients developed ocular disease requiring intravenous methylprednisolone therapy.[22]

Summary and Recommendations. Taken together, these data suggest that patients with posterior segment involvement from ocular Behçet disease should be treated with immunosuppressive drugs as early as possible in their course (AI; see Table 1). Azathioprine (BI), cyclosporine (BI), and the alkylating agents chlorambucil and cyclophosphamide (BII), all appear to be effective. However, none of these agents appears to be universally effective. Treatment with alkylating agents may have the potential for long-term, drug-free remissions, but these data come from uncontrolled case series rather than from randomized controlled clinical trials (BII). The choice of agents will depend on the patient and other features, including the activity of the other manifestations of Behçet disease, the presence of neurologic disease, renal function, fertility issues, and bone marrow status.

• **BIRDSHOT RETINOCHOROIDOPATHY:** *Clinical Features.* Birdshot retinochoroidopathy is a clinically distinct but uncommon form of chronic posterior uveitis characterized by bilateral, multiple, hypopigmented postequatorial retinal pigment epithelial and choroidal inflammatory lesions, with associated inflammatory cells in the vitreous. The cause is unknown, but its strong association with the HLA-A29 phenotype suggests that it may be an autoimmune disease. Patients with birdshot retinochoroidopathy commonly present with complaints of painless vision loss, especially nyctalopia, and with complaints of vitreous floaters. Disturbances in color vision also are common, and visual complaints are often out of proportion to the measured visual acuity, indicating diffuse retinal dysfunction, which can be documented by electroretinography. The most common complication of birdshot retinochoroidopathy is chronic cystoid macular edema, occurring in over 50% of cases, and macular edema is the most frequent cause of reduced central visual acuity. Epiretinal membrane formation occurs in at least 10% of cases, and 6% of patients may eventually develop breaks in Bruch membrane, allowing the development of subretinal choroidal neovascularization.[93–95]

Clinical Experience with Immunosuppressive Drugs. A definitive strategy for the care of patients with birdshot has not been established, and the mainstay of treatment has been the use of either periocular or systemic corticosteroids. However, the efficacy of such therapy has been inconsistent, and given the chronicity of this disease, the complications of repeated or chronic corticosteroid use may be problematic. In one series, less than 15% of patients treated with systemic corticosteroids achieved an adequate clinical response and were able to be maintained on low to moderate doses of prednisone.[96]

Uncontrolled case series have suggested that cyclosporine may be effective for birdshot retinochoroidopathy.[96–99] Compared with corticosteroid therapy alone, Vitale and associates[97] found that vitreous inflammation was controlled in 85% of the patients treated with cyclosporine, and visual acuity improved or stabilized in 83%. In contrast, 54% of patients treated with corticosteroids alone experienced a deterioration in visual acuity over the follow-up period. Treatment typically lasted for 24 to 48 months.

• **MULTIFOCAL CHOROIDITIS WITH PANUVEITIS:** *Clinical Features.* Multifocal choroiditis with panuveitis is an idiopathic, bilateral, ocular inflammatory disease. The appearance of the chorioretinopathy is similar to that produced by the presumed ocular histoplasmosis syndrome, but with more widespread chorioretinitis and, unlike the presumed ocular histoplasmosis syndrome, with vitreal inflammation. The clinical characteristics of multifocal choroiditis with panuveitis include panuveitis, with anterior chamber cells, vitreal cells, and round to ovoid chorioretinal lesions, ranging from 50 to 200 μm in diameter, scattered throughout the entire retina. In the resolving phase from active inflammation, the perimeter of the lesions becomes pigmented, and the lesions take on a "punched out" appearance. The disease tends to be chronic and vision damaging. Vision-limiting consequences include chronic macular edema, subretinal neovascularization, and optic neuropathy.[100–103]

Clinical Experience with Immunosuppressive Drugs. The natural history of the disease is one of great chronicity, with a high rate of vision loss.[102] Conventional therapy for multifocal choroiditis has been with corticosteroids, most often oral corticosteroids, and this form of treatment appears to be moderately effective with response rates at 50% or more.[103] However, because of the chronicity of the disease, the rate of corticosteroid-induced side effects may be high. Nussenblatt and associates[104] have stated that in their experience "at least the consideration of addition of other immunosuppressive agents" is a common decision

that has to be made at some point in the care of patients with multifocal choroiditis with panuveitis.

• **SERPIGINOUS CHOROIDOPATHY:** *Clinical Features.* Serpiginous choroidopathy generally presents with scotoma, decreased central vision, or metamorphopsia. The eye does not appear inflamed. The characteristic findings early in the disease are gray-white to yellow-white subretinal fundus lesions, beginning in a peripapillary location and spreading centrifugally. There usually is evidence of inactive disease in the other eye; disease progression is often asymmetric. As the disease progresses, these lesions coalesce into a serpentine formation, with pigmentary changes in the retinal pigment epithelium, and atrophy of the underlying choriocapillaris and choroid. Fluorescein angiography demonstrates typical early blocking with late staining of lesions. Serous retinal detachment, subretinal neovascularization, and subretinal fibrosis are late complications of the disease.[105–108]

The natural history is asynchronous, bilateral progression over many years. Disease progression tends to be episodic and recurrent. Flare-ups, with extension of existing lesions or development of new lesions, occur for several months at a time. Disease activity may recur after months of remission. Acute lesions cause absolute scotomata, which will cause loss of central vision if progression proceeds into the fovea; some recovery of scotomata has been noted in cases where there is minimal progression. No large studies have documented the risk of central vision loss in this disease, but current estimates of vision loss are 50% with long-term follow-up.[105–107]

Clinical Experience with Immunosuppression. No consensus exists for the treatment of serpiginous choroidopathy, and there is a scarcity of data in the literature. Descriptions of the clinical effect of oral or periocular corticosteroid medication are inconsistent, with some authors reporting clinical response in small case series[108] and others unable to demonstrate effect.[84] In those cases showing response, clinical effect was generally seen after 1 month of treatment; because the disease can spontaneously remit over the same time course, the efficacy of treatment in these cases is unclear. Uncontrolled case series have suggested that cyclosporine monotherapy may be successful,[109] but not all cases have been treated successfully.[110] One small series of five eyes treated with triple immunosuppression (prednisone 1 mg per kg per day, cyclosporine 5 mg per kg per day, and azathioprine 2 mg per kg per day) reported resolution of activity within 2 weeks of initiation of therapy in all affected eyes. Two eyes rapidly developed recurrences on weaning of medication, but both responded promptly to reinitiation of therapy.[84] The need for triple immunosuppression is unknown, because no cases treated with combination azathioprine and prednisone have been reported in the literature.

Summary. The posterior uveitides, birdshot retinochoroidopathy, multifocal choroiditis with panuveitis, and serpiginous choroidopathy, all appear to have a poor long-term outcome history and variable benefit from corticosteroid therapy. Although chronic corticosteroid therapy may control the disease in some patients, many patients may require an immunosuppressive drug (BIII). The most frequently used drug has been cyclosporine (II), although combination immunosuppressive drug therapy appears to be effective for serpiginous choroidopathy (II). It has been the experience of some panel members that alkylating agents may be of benefit for these disorders (III).

• **SCLERITIS:** *Clinical Features.* Scleritis is a severe, painful, and potentially sight-threatening disorder, often associated with an underlying systemic disease. Scleritis can be divided into anterior and posterior disease. Anterior scleritis has been further classified into the following categories: diffuse, nodular, necrotizing, and scleromalacia perforans.[111] Scleritis is characterized usually by pain and by redness of the sclera and episclera. Scleritis is bilateral in over 50% of patients but frequently starts in one eye. Necrotizing scleritis is a severe form of the disorder, frequently associated with both blinding ocular disease and life-threatening systemic disease.[111–113] An associated systemic autoimmune disease is present in 40% to 50% of the patients with scleritis.[111,112] Inflammation leads to scleral thinning, allowing the underlying choroid to become visible. Uveitis is often associated with severe cases of scleritis.

Scleritis has been associated with several forms of systemic necrotizing vasculitis, including Wegener granulomatosis and polyarteritis nodosa. Necrotizing scleritis is thought to be associated with more severe disease in patients with rheumatoid arthritis[112] and may be an indication for systemic immunosuppression in these patients. Wegener granulomatosis is a multi-organ disease characterized by a necrotizing granulomatous vasculitis. The disease involves the kidneys and respiratory tract; the eye is involved in over 50% of patients. Polyarteritis nodosa is also a systemic vasculitis that affects small-sized and medium-sized arteries and is associated with visceral organ involvement, myalgia, peripheral neuropathy, and renal disease. Like Wegener disease, eye involvement can occur.

Clinical Experience with Immunosuppression. Oral nonsteroidal anti-inflammatory drugs may control inflammation in mild cases of anterior scleritis. For more severe forms of the disease, oral corticosteroids or systemic immunosuppressive agents often are required.[111,113] The scleritis associated with necrotizing systemic vasculitis may be diffuse, nodular, or necrotizing, and treatment with immunosuppression is required to control the underlying vasculitis, because mortality is high in untreated patients.[56–59]

Necrotizing scleritis is difficult to treat and nearly always requires systemic immunosuppressive therapy.[113]

There are no randomized, controlled clinical trials of treatment for scleritis. Several studies have evaluated treatment of scleritis associated with necrotizing systemic vasculitis. Treatment of scleritis in patients with necrotizing systemic vasculitis should be guided both by the ophthalmic response and control of the underlying disease. The antineutrophil cytoplasmic antibody test may be a useful laboratory measure of the therapeutic response in patients with Wegener granulomatosis. Cyclophosphamide, starting at a dose of 2 mg per kg per day, is the drug most often used for necrotizing systemic vasculitis (AII) and is often used for refractory necrotizing scleritis (BII). Concomitant prednisone at a dose of 1 mg per kg per day is needed for initial therapy. Oral corticosteroids usually can be tapered and often discontinued over the first 2 to 4 months of cytotoxic therapy. Other immunosuppressive agents, including methotrexate, azathioprine, cyclosporine, and chlorambucil, have been used successfully for the treatment of necrotizing systemic vasculitis, but reports are anecdotal (BIII).

• **MUCOUS MEMBRANE PEMPHIGOID:** *Clinical Features.* Mucous membrane pemphigoid (previously known as cicatricial pemphigoid) describes a group of chronic autoimmune disorders affecting the mucous membranes. Although skin involvement may occur, it is present in a minority of patients (approximately 20%). Oral mucous membranes are involved most commonly, and ocular involvement occurs in approximately 80% of patients. The characteristic immunopathologic feature of mucous membrane pemphigoid is the linear deposition of immunoglobulin or complement at the epithelial basement membrane zone of mucous membranes, such as the conjunctiva.

The clinical features of ocular mucous membrane pemphigoid are chronic conjunctivitis, sometimes unilateral at first, but eventually bilateral, resulting in chronic scarring (cicatrization) with progressive subepithelial fibrosis, fornix foreshortening, symblepharon, trichiasis, distichiasis, and keratopathy. The end result is corneal scarring, neovascularization, and ulceration. The natural history of the disease is that of slow progression with only rare cases going into long-term sustained spontaneous remissions. The eventual result is progression to bilateral blindness.[64,114] Topical and local therapies have failed to halt the progression of the disease.

Clinical Experience with Immunosuppressive Drugs. Although corticosteroids may halt the progression of the disease, high doses are required, and the disease recurs with tapering oral corticosteroids.[64] Dapsone is effective for improving the symptoms and may control conjunctival inflammation for a period of time[115]; however, long term, most patients escape control with dapsone alone. Uncontrolled case series[63,114] suggested that oral daily cyclophosphamide was effective in controlling mucous membrane pemphigoid affecting the conjunctiva. Subsequently, a randomized, controlled study[64] confirmed these observations. Better control of the disease was established with the use of oral daily cyclophosphamide and oral corticosteroids than with corticosteroids alone, and the corticosteroids were successfully tapered in those patients given cyclophosphamide. In addition, after 12 to 18 months of treatment with cyclophosphamide, some patients may enter a long-term, drug-free remission.

Summary. The natural history of mucous membrane pemphigoid with ocular involvement is poor, and systemic anti-inflammatory medications are required (AII). Although corticosteroids, dapsone, and other immunosuppressive drugs may be of benefit, for those with severe disease, the alkylating agent cyclophosphamide appears to be most effective (BI). It is the opinion of some members of the panel that for patients with ocular involvement from mucous membrane pemphigoid who experience bladder toxicity from cyclophosphamide, chlorambucil may be substituted successfully (BIII). Experience with other immunosuppressive agents for mucous membrane pemphigoid is limited, but antimetabolites may have value in selected patients (BIII), particularly those who cannot tolerate alkylating agents. However, some clinicians consider them less effective than the alkylating agents in this situation.

BIOLOGICS AND FUTURE DIRECTIONS

THE BASIC UNDERSTANDING OF THE IMMUNE SYSTEM IS rapidly improving. With new insight, new pharmaceutical approaches are being been designed (Table 4), sometimes referred to as biologics. Examples include monoclonal antibodies to proteins, such as cytokines (for example, tumor necrosis factor-α), cell adhesion molecules, cytokine receptors (anti-interleukin-2 receptor), or T-cell subsets (anti-CD4). Soluble tumor necrosis factor receptors, such as etanercept (Enbrel; Immunex, Seattle, Washington), for tumor necrosis factor inhibition are now in clinical use. As of June 2000, a naturally occurring interleukin-1 receptor antagonist was undergoing evaluation for the treatment of rheumatoid arthritis. Additional new approaches to immunosuppression include leflunomide (Arava; Aventis Pharma USA, Parsippany, New Jersey), an antimetabolite that may have T-lymphocyte specificity, immunoadsorption columns, and intravenous immunoglobulin. Oral tolerance is based on the premise that the immune response can be inhibited systemically by oral exposure to an antigen.

Nonophthalmic Studies. Etanercept has had success in the treatment of rheumatoid arthritis and juvenile rheumatoid arthritis, and currently is being studied for other

TABLE 4. Biologic Agents for Immune Modulation

Class	Generic Name (Trade Name)	Initial Dose	Maximum Dose	Mechanism	Expected Onset	Representative Side-effects	Comments
Cytokine inhibitors	Etanercept (Enbrel)	25 mg 2×/week SC*		TNF inhibition: soluble TNF receptor	1–8 weeks	Sepsis, lymphoma, autoantibodies, skin reactions, cost	
	Infliximab (Remicade) antibody	3 mg/kg/day IV Q 8 weeks†	10 mg/kg IV Q 4 weeks	TNF inhibition: α-TNF monoclonal antibody	1–8 weeks	Sepsis, lymphoma, autoantibodies, cost	
	Daclizumab (Zenapax)	1 mg/kg IV Q 2 weeks × 5 (renal transplant dose)		IL-2 inhibition: α-IL-2 receptor antibody	Days	Granulomatous inflammation, infection, cost	Phase I for uveitis done; main indication is transplant

IL-2 = interleukin-2; TNF = tumor necrosis factor. Other abbreviations as in Table 2.
*The pediatric dose is 0.4 mg/kg twice per week.
†Infliximab is administered at 0, 2, and 6 weeks before the maintenance schedule of every 8 weeks.

immune-mediated diseases. Antibodies to CD4 or to the interleukin-2 receptor have been beneficial in treating acute transplant rejection. Leflunomide has been approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis. The immunoadsorption column also is approved for the treatment of rheumatoid arthritis, but extrapolating this result to diseases not characterized by a similar contribution from immunoglobulin is problematic. Intravenous immune globulin has shown modest benefit in specific immune-mediated diseases, such as Guillain-Barre syndrome and idiopathic thrombocytopenic purpura. Trials of additional biologic or immunomodulatory drugs are ongoing for other potentially novel targets within the immune system.

Clinical Experience for Inflammatory Eye Disease. One small, uncontrolled case series found that daclizumab (Zenapax; Roche, Basel, Switzerland), a monoclonal antibody to the interleukin-2 receptor (anti-Tac), facilitated the reduction in immunosuppressive therapy for patients with uveitis.[116] One small, randomized controlled trial on oral feeding with retinal S antigen demonstrated equivocal benefit in patients with uveitis.[117] Additional trials have been halted because of a dearth of available antigen. One small, uncontrolled case series reported that approximately 50% of patients with uveitis that was refractory to immunosuppressive medication could benefit from intravenous immune globulin.[118] Interferon α-2B appeared to be of value for ocular Behçet disease in a randomized controlled clinical trial.[119] Studies evaluating the use of etanercept in the treatment of uveitis associated with juvenile rheumatoid arthritis and the use of leflunomide for uveitis in adults are ongoing as of June 2000.

Adverse Events and Monitoring. Toxicity depends on the individual medication. Etanercept has been associated with local injection site reactions and rarely with serious infections. Concern remains with regard to the inhibition of tumor necrosis factor and the risk of malignancy development. Intravenous immune globulin is associated with headaches, malaise, thrombophlebitis, sterile meningitis, and serious vaso-occlusive events, such as stroke. Immunoglobulin is a blood product that could potentially transmit infection.[118] Anti-interleukin-2 receptor therapy for uveitis has been associated with rashes, edema, granulomatous reactions, and viral respiratory infections.[116]

Summary. It is hoped that one day we will regard current nonspecific approaches to immunosuppression as having too nonselective an effect and as being too toxic and that we will be able to use more selective immunomodulating agents. Etanercept currently is the most widely used biologic, and its use to treat rheumatoid arthritis has been marked by substantial clinical response. At present, the use of biologics to treat uveitis is restricted because of

lack of adequate clinical experience, but ongoing studies may change this recommendation.

PREGNANCY AND CHILDREN

BECAUSE OF THE POTENTIAL FOR TERATOGENICITY OR THE lack of sufficient data to evaluate safety in pregnancy, appropriate contraception should be employed throughout the duration of any immunosuppressive drug use. Methotrexate is a teratogenic and, at high doses, an abortifacient. For methotrexate, there is a suggestion that its use in men may increase the possibility of malformations should they father children while on methotrexate. As such, it is prudent to continue contraception for 3 months after discontinuation of methotrexate in men and for at least one ovulatory cycle in women. As noted above, alkylating agents are not only teratogenic, but may cause sterility. For mycophenolate and tracolimus, there are insufficient data to evaluate their use in pregnancy. Because it is an antimetabolite, concerns persist that azathioprine may be teratogenic. Although azathioprine is best avoided during pregnancy, large-scale studies in transplant patients have demonstrated that azathioprine may be fairly well tolerated during pregnancy, with the major neonatal risks being prematurity and small for gestational age neonates.[120] Although there are few data on cyclosporine's use in pregnancy, the available human data do not demonstrate a substantially increased risk of malformations. Some studies have suggested no increased rate of pregnancy complications, whereas others have suggested higher rates of spontaneous abortion, premature labor, and offspring that are small for gestational age.[120] Prednisone appears to be the safest, most widely used, and best-tolerated systemic anti-inflammatory drug for use in pregnancy. Although animal studies have shown an increased rate of clefting with superpharmacologic dosing, human studies have failed to substantiate any significant teratogenic effects.[120] Use of oral corticosteroids in pregnancy should be carefully coordinated with the patient's obstetrician.

Children receiving systemic corticosteroids or immunosuppressive drugs require special attention because of the effect of these agents on growth, nutrition, school and recreational activities, infectious diseases, and fertility. Unique to children is the effect of treatment on growth and development.[5] Suppression of growth by corticosteroids is dose related; for most children, growth will cease completely at doses greater than 2 mg per kg per day or 40 mg per M^2 per day. Growth suppression cannot be reversed with human growth hormone. Immunosuppressive drugs do not affect linear growth directly but can interfere with nutrition, and thus growth indirectly, by causing nausea, abdominal pain, or anorexia. All children on oral corticosteroid therapy should have height and weight measured regularly (for example, at 3-month intervals) and recorded on a growth curve.

Other effects of corticosteroids in children include osteoporosis and adrenal suppression. As with adults, children receiving long-term systemic corticosteroids should be given calcium and vitamin D to reduce bone mineral loss. Secondary Cushing syndrome occurs with variable degrees in all children given moderate to high doses of prednisone. The ability of children receiving chronic corticosteroid or immunosuppressive drug therapy to participate in school and recreational activities is a common concern. In general, children can engage in these activities. Contact sports may not be appropriate for some children, however, especially if they have arthritis, because of the risk of injury to bones and joints. Although corticosteroids may result in poor wound healing, this issue has not been a major problem for most children during treatment.

Methotrexate is the most common immunosuppressive agent used in children. It is generally safe, well tolerated, and easily administrated. It is metabolized more rapidly in children than in adults, and thus, doses must be higher, on a per-weight basis, in children than in adults. Methotrexate usually is given to children once weekly at an oral dose of 10 to 25 mg per M^2. Because children are smaller, total weekly doses generally are in the same range as those given to adults (7.5 to 15 mg per week). Absorption is variable in children, and subcutaneous injection of methotrexate should be considered before assuming that maximally tolerated therapy is ineffective. Subcutaneous injections may also be better tolerated than oral administration in children who experience stomach upset with oral methotrexate.

Methotrexate is an effective treatment for juvenile rheumatoid arthritis.[121] Methotrexate also has been reported in small, uncontrolled case series to be an effective treatment for the uveitis associated with juvenile rheumatoid arthritis[122] and for the similar chronic, noninfectious anterior uveitis of childhood that can occur in the absence of joint disease. Aggressive anti-inflammatory treatment of such cases, with chronic suppression of ocular inflammation, is warranted in an attempt to prevent ocular complications, such as posterior synechiae, secondary glaucoma, secondary cataract, macular edema, and band keratopathy, which occur commonly with untreated disease.

Cyclosporine also has been used to treat various forms of uveitis in children.[49,122] Small, uncontrolled case series have suggested that cyclosporine may be effective for treatment of intermediate uveitis and panuveitis in children.[122] In one small, uncontrolled case series cyclosporine was not effective as monotherapy for treatment of the uveitis associated with juvenile rheumatoid arthritis[49]; however, cyclosporine sometimes is added to methotrexate for the treatment of inflammatory eye disease, when methotrexate, at tolerable doses, is incompletely effective as monotherapy.

Although alkylating agents have been used in children for the treatment of life-threatening disorders, such as

severe systemic lupus erythematosus, Behçet disease, and other systemic vasculidities, the potential for serious long-term side effects has limited their use for non–life-threatening diseases, such as uveitis. Thus, there is little experience in the treatment of ocular inflammatory disease with these agents.

Communicable diseases are a concern for immunosuppressed children because of their increased exposure to infectious diseases from other children. Most immunosuppressive agents interfere with cellular immunity rather than antibody-mediated immunity. Thus, children receiving these agents are not particularly susceptible to respiratory infections and do not need to be isolated from other children. Nevertheless, because these children are more likely to develop systemic viral diseases, they should receive a yearly influenza vaccine, and if susceptible, varicella-zoster virus immune globulin upon close exposure to chickenpox. If the CD4+ T-lymphocyte count is less than 200 cells per μl, consideration should be given to placing the child on *P. carinii* prophylaxis.

Children receiving high-dose corticosteroids or immunosuppressive drugs should not receive live virus vaccine (MMR vaccine, varicella-zoster virus vaccine, oral polio vaccine, BCG) while on therapy for 3 months after stopping therapy. If possible, varicella-zoster vaccine should be given before the start of therapy. Children receiving only corticosteroids at doses less than 20 mg prednisone daily, or for children less than 10 kg body weight less than 2 mg per kg per day of prednisone daily, can be given live virus vaccines.

Compliance may be a problem in long-term drug therapy of children and adolescents. Problems of weight gain, acne, and mood swings may be particularly troubling to teenagers, who are notable for stopping their own medications. Parents or guardians must participate in the administration of medications to assure that doses are not missed.

CONCLUSIONS

ORAL CORTICOSTEROIDS REPRESENT ONE OF THE MAINstays in the treatment of severe ocular inflammation. However, chronic oral corticosteroid therapy is associated with several potential side effects, which may have adverse effects on the patient's long-term health. Therefore, many patients on chronic oral corticosteroids will require the addition of an immunosuppressive drug, either because of the occurrence of these side effects or because of the need for a dose of oral corticosteriods highly likely to result in long-term side effects. In selected diseases, such as Behçet disease with posterior segment ocular involvement, the outcome of oral corticosteroid therapy alone is sufficiently poor that immunosuppressive drugs probably should be used from the outset. Because of the potential for side effects, and because of the different side effects of the different drugs, treatment must be individualized and regular monitoring performed. With careful use of these medications, many patients will benefit from them either with better control of the ocular inflammation or with a decrease in corticosteroid side effects.

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