utlizadas no tratamento de uveítes intermediárias e posteriores. Em muitos casos é difícil ter certeza se a injeção está sendo aplicada no espaço subtenoniano ou retro-bulbar.

Nossa conduta básica em relação à via de administração de corticóide em uveítes é a seguinte: Uveíte Anteriores-Tópica, Sistêmica (e Peri-ocular). Uveítes Posteriores Sistêmica, (tópica e periocular). Uveíte Intermediária-Periocular (sistêmica e tópica). Uveíte Difusa-Sistêmica, Tópica (e periocular).

Em muitas uveítes o corticóide não basta para controlar a inflamação, como por exemplo, casos de Behçet e Vogt-Koyanagui-Harada. Assim, devem ser empregados outros agentes como a colchicina ou drogas citotóxicas. Desta maneira, evita-se o emprego de altas doses de corticóide, que são as mais iatrogênicas.

Outro aspecto importante no tratamento com corticóide diz respeito à necessidade de retirada lenta tanto por via tópica quanto sistêmica, para evitar-se o mecanismo de "rebote".

REFERÊNCIAS

1. SAARI, K. M. — Uveitis Update. Int. Symp on Uveitis. Amsterdam, Excerpta Medica, 1984.
2. SCHLAEGEL, T. F. JR. — Current Aspects of Uvetiis. Int. Ophthal Clin., 17: 1-16, 1977.

Immunosuppressive Agents and New Approaches to Medical Therapy

Robert B. Nussenblatt, M.D.*

Though corticosteroids are the mainstay of therapy for severe intra-ocular inflammatory disease, other medications can certainly be considered. Probably the most widely utilized after corticosteroid therapy are cytotoxic agents. Several reports in the literature have suggested the beneficial aspects of immunosuppressive therapy with cytotoxic agents in well selected patients. The cytotoxic agents most often used in ophthalmic inflammatory disorders would fall into the category of either alkylating agents or anti-metabolites. Both of these categories of cytotoxic agents have effects that are not limited to the immune system. Indeed, their effect will be on any dividing cell, particularly those that divide rapidly. The alkylating agents appear to cross link DNA, thereby preventing them from acting as a template for cellular function. The anti metabolites effect the cell division cycle in a different manner. This group of agents will enter into the DNA precursor cycle and thereby alter ultimately the DNA being formed. Since this DNA is not "perfect" then cellular function will not be able to continue.

Indications for Therapy:

In 1980, the International Uveitis Study Group summarized its suggestions for the indications of cytotoxic therapy in intra-ocular inflammatory disease (Fig. 1). Behçet's disease with ocular involvement is considered an indication for cytotoxic therapy. In this disorder, it has been noted that long term corticosteroid therapy is ineffective in preventing the severe visual handicap that ultimately can be seen in these patients. An additional indication would be for patients who have sympathetic ophthalmia who are not responding well to corticosteroids. For Behcet's disease, the most widely used cytotoxic agents appear to be that of the alkylating variety. A second broad category would be in the case of other ocular inflammatory conditions of a non-infectious etiology that are responding poorly to systemic corticosteroids or that secondary effects have rendered the continued administration of this medication intolerable. It should be remembered that patients who will be treated with this therapeutic approach should be those who have disease that in the best estimation of the ophthalmologist can be reversed with anti-inflammatory medication. Additionally, the indication for therapy should be clear in the ophthalmologist's

INDICATIONS FOR CYTOTOXIC AGENTS IN THE TREATMENT OF INTRA-OCULAR INFLAMMATORY DISEASE
International Uveitis Study Group — 1980.

Absolute:	Behcet's disease. Sympathetic ophthalmia, if severe, and not responding to steroid.
Relative:	Noninfectious uveitis unresponsive to maximum systemic corticosteroid therapy.
Contraindications:	Focal chorioretinitis, herpetic, CMV and fungal retinal disease, toxoplasmosis.

* National Eye Institute. National Institutes of Health. Bldg. 10, Rm. 10N202. Bethesda, MD 20205.

mind so that criteria to determine whether the patient has responded or not to this therapeuic approach can be readily evaluated.

Dosages:

Chlorambucil is usually given at a dose of 0.1 to 0.2 mg/kg. An effective dose is usually reached between 6 8 mg po and only after several weeks. A lower dose is initially administered to be sure that idiosyncratic effects will not be seen. A daily dose above 8 mg may be needed in some cases, but must be given very cautiously. The initial therapeutic dose of Cyclophosphamide is 1-2 mg/kg/day. This is decreased as an immunosuppressive effect is seen, i.e. a drop in the peripheral white count. A response to the cyclophosphamide regimen is usually seen somewhat more rapidly as chlorambucil. Asothioprine is usually given in the dosage of 2.02.5 mg/kg/day. All of these drugs can be given in conjunction with steroids. Often patients will need both steroids and one of these agents to fully suppress their ocular inflammatory disease.

Contra-indications:

Evidence of acute or chronic infection or an underlying hematologic abnormality in a patient would not permit the use of these agents. A major complicating factor as well would be that of an underlying neoplasm. Though some of these medications have been used while patients have been pregnant, the teratogenicity of these drugs is a real possibility. The long-term effect on patients who have received immunosuppressive therapy of this nature is still not clear. A real potential risk exists for the development of a neoplasm. Additionally, recent evidence would suggest that long term alkylating agent therapy will induce permanent chromosomal damage in these individuals. Therefore, it has been suggested by some that alkylating agent therapy cannot be administered for longer than approximately 2-3 years. Additionally, these agents will induce sterility.

Complications:

Frequent blood counts with special attention to the white count, differential and platelets are manditory. Though a moderate leukopenia is a reasonable goal for this therapy, particularly with the alkylating agents, all these medications can potentially cause severe bone marrow alterations.

Additionally, infections due to opportunistic organisms such as fungus and virus can be seen. The possibility of a secondary neoplasm has already been discussed. More specifically, certain secondary effects have been associated with certain of these medications. For instance, Chlorambucil has been associated with pulmonary fibrosis, liver toxicity, rash, and sterility while Cytoxan has been associated with alopecia, male and female sterility, pulmonary fibrosis and hemorrhagic cystitis and Asothioprine has been associated with liver and gastrointestinal toxicity as well as rash and fever.

Another drug which has received recent notability has been that of Cyclosporine. Cyclosporine is a natural product of the fungus Tolypocladium inflatum Gams. Its mode of action is not through cytotoxicity. Additionally, the drug appears to have its effect limited to the immune system itself. The vast bulk of its action appears to be on the interruption of T cell interactions. More specifically, it appears to inhibit the release of various lymphokines that are important in the augmentation of an immune response through the recruitment of various immune cells including T-cells.

Indications:

Indications for the use of Cyclosporine would be in those individuals who have bilateral sight threatening intermediate and posterior uveitis of a noninfectious etiology. It should be emphasized that Cyclosporine's efficacy and safety is still being evaluated and if this drug is to be utilized it should be utilized in conjunction with an individual who has aproval for ts use and in patients who have failed other more standard therapeutic approaches. We have noted the drug to be particularly beneficial in the treatment of patients with Behcet's disease. Additional diseases which appear to respond to Cyclosporine have been that of pars planitis, sympathetic ophthalmia and Vogt-Koyanagi-Harada's disease.

Complications:

The complications of this drug include: hypertension, increased hair growth, tingling sensations of the extremities, increased hot and cold sensitivities of the extremities. In our experience, the most important, and at times limiting complication, has been that of nephrotoxicity. Lymphoma has been reported in a small number of patients, but the direct association of Cyclosporine to lymphoma has not been established. It would appear that in the patients who develop lymphoma, the vast majority were treated with other immunosuppressive agents thereby

making the evaluation of the role of Cyclosporine in their disease difficult to determine.

Contraindications:

The contraindications for this medication would be essentially the same as those for patients who are being considered for cytotoxic agent therapy. It should be emphasized that the patient should be evaluated by an individual who has had experience with this medication. Particular contraindications would include hypertension and long standing renal disease. Additionally, patients over the age of 60 would be poor candidates for this medication because of their markedly decreased renal reserve. In individuals past the age of 60, the potention for long term Cyclosporine use to treat their problem diminishes dramatically.

Dosages:

Generally a initiating dose of 10 mg/kg is given orally per day. In general this dose is administered once a day. The medication needs to be diluted in large quantities of either non citrid juices or chocolate milk. This dose needs to be titrated based on Cyclosporine plasma levels as well as the therapeutic response and secondary effects that are seen.

Other Therapeutic Modalities:

Several other therapeutic modalities have been reported as potentially useful in the treatment of intra-ocular inflammatory disease (Fig. 2). Four patients with endo-

PROPOSED THERAPEUTIC MODALITIES IN UVEITIS

Observation.		
Immunosuppressive	Nonspecific.	
	Specific.	
Plasmapharesis		
Immunostimulation	Levani sale	BCG
	Transfer Factor	Interferon
Centibiotics		
Surgery	Cryosurgery	Vitrectomy
	lensectomy	
Nutrition and Social Habits Alterations		
Allergy Therapy		

genous uveitis of a noninfectious origin, it would appear that immunostimulators are not effective in the therapy of these disorders. Additionally, the use of transfer factor has been suggested as being useful, but this has never been carefully evaluated. In one report the utilization transfer factor for Behcet's disease had a negative effect. Plasmapheresis has been reported to effectively treat the acute episodes of Behcet's disease. Full evaluation of this mode of therapy needs also to be done. In the treatment of other nonocular ailments the use of plasmapheresis is usually combined with systemic cytotoxic agent or steriod therapy.

The future remains quite bright in the field of therapeutics for ocular inflammatory disease. Newer medications which will hopefully be more specific in their approach appear to be reasonable goals. The use of cloning techniques in both cellular and molecular should open many doors in the development of these therapeutic approaches