

Received: 2005.02.15
Accepted: 2005.04.12
Published: 2005.12.15

Immunotherapeutic approaches in ocular inflammatory diseases

Shree K. Kurup and Chi-Chao Chan

National Eye Institute, National Institutes of Health, Bethesda, MD 20892-1857, USA

Source of support: self financing

Summary

This comprehensive review discusses immunotherapeutic approaches to ocular inflammatory diseases, updates information provided in the literature, and presents clinical experiences with an emphasis on autoimmune uveitis at the National Eye Institute, United States. Current medical and surgical therapeutic approaches, including medications such as corticosteroids, anti-metabolites, alkylating agents, calcineurin and purine synthesis inhibitors, biologics as well as some anti-infectious agents, are reviewed along with new modalities and experimental approaches. Most immunosuppressive therapies have significant adverse effects. Physicians must be familiar with the pharmacology of the available drugs and aware of the philosophies behind the treatment.

Key words:

inflammation • uveitis • autoimmune diseases • immunosuppressive medications • adverse effect • therapy

Full-text PDF:

http://www.aite-online/pdf/vol_53/no_6/8422.pdf

Author's address:

Chi-Chao Chan, M.D., Laboratory of Immunology, NIH/NEI, Bldg. 10, Rm. 10N103, 10 Center Drive, Bethesda, MD 20892-1857, USA, tel.: +1 301 496-0417, fax: +1 402 402-8664, e-mail: chanc@nei.nih.gov

INTRODUCTION

Ocular inflammatory diseases are defined as acute or chronic inflammation of the ocular tissues and represent the fourth leading cause of blindness in the United States after age-related macular degeneration, glaucoma, and diabetic retinopathy^{2, 57}. They can present in acute (less than 6 weeks) or chronic forms⁵⁷. Ocular inflammatory disease is also loosely termed uveitis, although areas of inflammation may include the retina and sclera in addition to uveal tissue (the iris, ciliary body, and choroids). The purpose of this review is to briefly summarize the philosophy and principles of management of different ocular inflammatory diseases, with a focus on new therapeutic options. In the United States, the only drug class currently approved by the Food and Drug Administration (FDA) for use in ocular inflammatory conditions (diseases) is corticosteroids. While there are many more options today than before, choices of therapy must be guided by the clinical indication and individual patient characteristics. These include the patient's need, ability to adhere to therapy, and compliance with follow-up visits. Infection and neoplasm may induce autoimmune responses and this must be carefully considered^{11, 18, 23, 64}. All of these factors are critical, as the majority of these immunosuppressive agents are extremely potent and have significant adverse effects^{2, 7, 46}. Drugs are typically started at low doses and then titrated carefully to full effect.

NOMENCLATURE AND TERMINOLOGY

Uveitis

In this review “uveitis” is used interchangeably with “ocular inflammatory disease or condition” and indicates inflammation in any intraocular tissue.

Cell, flare, and haze

These terms refer to increasing severities of uveitis. Active intraocular inflammation frequently manifests as inflammatory cells, predominantly neutrophils and macrophages, freely floating in the aqueous chamber; it usually is associated with an increase in the viscosity of the aqueous, termed **flare**. When the inflammation is present in the vitreous humor, it manifests as loosely floating cells that are often associated with various degrees of clouding, termed **haze**.

Anterior uveitis is defined as intraocular inflammation restricted to the anterior segment of the iris, ciliary body, and aqueous humor. Intermediate uveitis involves mainly the pars plana, and anterior vitreous

humor and may be coexistent with cystoid macular edema. A diagnosis of posterior uveitis indicates inflammation involving the posterior pole with choroiditis, retinitis, retinal vasculitis, vitritis, and/or retinal/choroidal neovascularization. These anatomic definitions may overlap occasionally.

Systemic

A condition or mode that affects the entire body.

Local

A process and/or therapy limited to the eye(s). This includes a periocular or an intravitreal injection.

Periocular

Administration of a medication in the tissues around the globe.

PHARMACOTHERAPEUTIC AGENTS

Glucocorticoids

Glucocorticoids (corticosteroids) are multifunctional hormones that suppress inflammation and certain immunologically driven processes by influencing target genes^{48, 68}. Prednisone (equivalent to prednisolone) is the prototypical agent used in ocular immunology and uveitis that is typically administered orally at 0.25–0.75 mg/kg/day in the morning and tapered in a standard manner⁵⁷. From an average dose of 40 mg per day for severe uveitis, it is generally tapered off by a decrease of 10 mg every two weeks. At 20 mg daily, further decrease is by 2.5–5 mg every two weeks^{24, 26, 57, 70}. Lower doses are used for mild inflammation. Steroids can also be delivered as periocular (triamcinolone) or intraocular injections (triamcinolone, preferably preservative free).

Glucocorticoids form complexes with specific receptors on the cell membrane that migrate to the cell nucleus where they interact with regulatory sites within DNA and modulate several genes involved in inflammatory and immune responses^{48, 70}. At the cellular level, glucocorticoids inhibit the migration of leukocytes and interfere with the functions of leukocytes, endothelial cells, and fibroblasts; at higher doses they have been demonstrated to suppress humoral factors involved in the inflammatory response^{48, 57}. The physician should be aware that the benefits of glucocorticoid therapy are offset by the debilitating adverse effects that can arise in the short and long term (Table 1). Minimizing the incidence and severity of glucocorticoid-related adverse effects

Table 1. Corticosteroids

Corticosteroid drug formulations					
Medication	equivalent, glucocorticoid, dose (mg)	relative potency		half-life	
		anti-inflammatory	mineralocorticoid*	plasma (min)	biologic (h)
Shorter-acting agents					
Cortisone	25	0	++	30	8–12
Hydrocortisone	20	0	++	90	8–12
Intermediate-acting agents					
Prednisone	5	+	+	60	12–36
Prednisolone	5	+	+	200	12–36
Triamcinolone	4	+	0	300	12–36
Methylprednisolone	4	+	0	180	12–36
Long-acting agents					
Dexamethasone**	0.75	++	0	200	36–54
Betamethasone	0.6	++	0	300	36–54

Adverse effects of corticosteroids

Relatively early in therapy:

- insomnia
- mood disturbances (children especially)
- increased appetite
- obesity
- acne vulgaris
- raised intraocular pressure, more so with periocular injections

Common in patients with co-existing drugs and toxicities:

- hypertension
- glucose intolerance or frank diabetes mellitus.
- peptic ulcer disease

Relatively later in therapy:

- hypothalamus-pituitary-axis suppression
- cushingoid habitus
- immunosuppressive action causing susceptibility to infectious agents
- delayed and poor wound healing
- osteonecrosis (avascular necrosis of the bone)
- steroid myopathy (reversible to great extent on discontinuation)

Insidious and delayed:

- cataracts
- skin atrophy
- osteoporosis (can also be early)
- accelerated atherosclerosis
- growth retardation (children)
- body fat redistribution
- fatty liver and hepatitis
- glaucoma

Other adverse effects, some of which are unpredictable:

- psychosis
- pseudotumor
- epidural lipomatosis
- pancreatitis

Revised from Boumpas et al.¹² and Brogan and Dillon¹³.

* Associated with most of the adverse effects such as weight gain and hypertension.

** Most potential to increase intraocular pressure.

requires carefully manipulating the dosage, using adjunctive corticosteroid-sparing immunosuppressive agents, and taking advance general preventive mea-

asures^{38, 48, 49, 57}. Recommendations for all patients on corticosteroids include exercise to maintain muscle mass, avoidance of other gastric irritants such as

NSAIDs, prophylactic use of an H-1 blocker or proton pump inhibitor, and calcium supplementation (for a person weighing 60 kg: 1500 of elemental calcium)¹² accompanied by vitamin D. In patients at high risk for osteoporosis, weekly biphosphonate therapy is indicated. Table 1 summarizes an overview of corticosteroids.

Anti-metabolites

Methotrexate (MTX). MTX is an anti-metabolite available in oral or injectable forms which has been used extensively in various ocular inflammatory conditions as one of the first-line immunosuppressive drug options. MTX inhibits dihydrofolic acid reductase and thus interferes with DNA synthesis, repair, and cellular replication, with actively proliferating cells being relatively more sensitive to its action⁷⁰. The exact mechanism of its action in autoimmune diseases is currently uncertain^{24, 70}. Although clinical effects of MTX typically are manifest after 4–6 weeks of therapy, its effect on blood counts may be visible as early as a week after initiation of therapy. MTX is well absorbed though variably so orally; bioavailability and clinical efficacy may be increased when injected subcutaneously or intramuscularly⁷⁴. Several non-randomized, uncontrolled studies document the utility of MTX in ocular inflammatory diseases, and one particular case series tended to favor its use in ocular sarcoidosis^{24, 26}. The maximum dosage used in uveitis ranges from 10–20 mg/m²/week (roughly equivalent to 15–25 mg/week for a person who weighs 60 kg). It is initiated at a lower dose; as patient tolerance increases it is increased by 2.5–5 mg/week until efficacy is achieved.

Pre-treatment with MTX assessment includes a complete blood count with differential, hepatic enzymes, renal function tests, and a chest X-ray. Periodic monitoring of these serum chemistry and blood counts are required: CBCs at least monthly, and renal and liver function tests every 1–2 months. Caution should be used when NSAIDs or cyclosporine are administered concomitantly with MTX due to the risk of renal toxicity. This is commonly the case when treating juvenile idiopathic arthritis (formerly juvenile rheumatoid arthritis) associated uveitis. Since folate-deficient states increase MTX toxicity, daily folic acid (1 mg or more) is essential while MTX is prescribed. Toxicities of MTX include stomatitis, gastritis, anemia (reflecting bone marrow suppression), hepatonecrosis and fibrosis⁴⁷, renal toxicities, and idiosyncratic pulmonary toxicity, occasionally progressing to pulmonary fibrosis. MTX is excreted via the kidney, is not dialyzable, and the physician must inform the patient about the dosing guidelines. A practical

approach to ensure relative safety is to limit the first prescription to 3 or 4 doses. The FDA classifies MTX as Pregnancy Category X (absolutely contraindicated) due to its teratogenicity (Table 2).

Table 2. FDA Classification of Drugs in Pregnancy

Category	Interpretation
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities in any trimester of pregnancy.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. OR No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant.

Source: FDA

Azathioprine (AZT). AZT is an immunosuppressive antimetabolite that is administered orally at 2–4 mg/kg/day for the management of ocular inflammatory disease. AZT is well absorbed following oral administration. Serum levels are of minimal predictive value for therapy since the magnitude and duration of clinical effects correlate with thiopurine nucleotide levels in tissues rather than with plasma drug levels. AZT and mercaptopurine are moderately bound to serum proteins (30%) and are partially dialyzable. Both compounds are rapidly eliminated from the blood and are oxidized or methylated in erythrocytes and liver; no AZT or mercaptopurine is detectable in urine after 8 h. Renal clearance is probably not important in predicting biological effectiveness or toxicities, although dose reduction is prac-

ticed in patients with poor renal function. AZT is mutagenic in animals and humans, carcinogenic in animals, may increase the patient's risk of neoplasia⁶⁹, and is Pregnancy Category D (Table 2).

The mechanisms of AZT's effect on autoimmune diseases are not entirely clear. AZT is immunosuppressive, with greater suppressive effects on delayed hypersensitivity and cellular cytotoxicity than antibody production at the recommended doses. Both the immunosuppressive and therapeutic effects are dose-related, but an optimal dose has to be individually tailored. AZT is a slow-acting drug (4–6 weeks) and its clinical and adverse effects may persist in the absence of its use^{22, 69}. The adverse effects of AZT include bone marrow depression, gastrointestinal upset, and hypersensitivity. AZT interacts with allopurinol, and thus the dosage of AZT needs to be decreased when the two drugs are used concomitantly. The use of angiotensin-converting enzyme inhibitors can also increase bone marrow toxicity in certain patients. There are several other drug interactions beyond the scope of this review that interfere with the clearance of AZT and are summarized elsewhere²⁷.

Alkylating agents

The guidelines for the application of alkylating agents in uveitis are listed in Table 3. The most common drugs are discussed here.

Table 3. Alkylating medications

Guidelines for the use of alkylating drugs in uveitis
Well-established diagnosis with risk-benefit ratio assessed
Severe, vision-threatening disease
Inadequate response to less toxic therapy
No infection or neoplasm
No pregnancy or possibility thereof
Informed consent obtained
Availability of adequate facilities to monitor and treat potential complications

Revised from Nussenblatt et al.⁵⁷.

Cyclophosphamide. Cyclophosphamide, a mustard gas derivative, is the inactive form of several alkylating agents which are formed as hepatic metabolites. These metabolites interfere with DNA replication and thus are cytotoxic, which is reinforced by the coexistent phosphorylating properties of the drug. Cyclophosphamide also possesses strong immunosuppressive activity and is utilized at 2–4 mg/kg/day orally in patients with non-infectious uveitis.

Similar to other cytotoxic agents, bone marrow depression and gastrointestinal toxicity are the most

important adverse reactions^{7, 67}. Nausea and vomiting often occur during treatment, and significantly decreased blood counts may manifest as early as 1–2 weeks. About 50% of patients treated with cyclophosphamide develop alopecia. Cyclophosphamide may cause a hemorrhagic cystitis due to its metabolites such as acrolein. Although adequate hydration with the use of oral or parenteral mesna (2-mercaptoethane sulphonate sodium) has been demonstrated to prevent cystitis, mesna has not been widely applied³⁶.

Irreversible amenorrhea and azoospermia have been reported as severe adverse effects^{57, 73}. Liver toxicity and idiosyncratic progressive pulmonary fibrosis with primary and secondary heart failure have also been reported. Cyclophosphamide has been linked to both bladder and hematological malignancies³⁹. The risk of these severe complications appears to increase dramatically with a cumulative dose of over 100 g; in one report, as many as 5% of all patients treated developed bladder cancer^{7, 13, 67}. Prescriptions in children should be only made in consultation with a pediatrician who has expertise in this field. Elderly patients will require dose adjustments based on calculated renal clearance. The mutagenic, teratogenic, and carcinogenic potential of these medications must be considered prior to administration of this drug in a fertile female because the consequences to an unintended pregnancy could be devastating (Table 4).

Table 4. Cyclophosphamide

Bioavailability	Little variability
• peak plasma level	• 1 h
• plasma half-life	• 4–10 h
• active metabolites*	• bioactive drug
• elimination**	• predominantly renal

* The effect of the drug is based on its metabolites, which also have short half-lives.

** 40% or more are excreted through the stool following oral administration.

The success of cyclophosphamide in ophthalmology is evident in the management of Wegener's granulomatosis (WG). WG is necrotizing granulomatous vasculitis that typically involves the orbits, upper and lower respiratory tracts, and the kidneys⁶⁷. Standard therapy for WG includes the daily administration of low-dose oral cyclophosphamide and corticosteroid therapy, which has dramatically improved the survival of patients with this otherwise fatal disease. More than 90% of patients treated with cyclophosphamide and corticosteroid therapy improve markedly, and 75% achieve prolonged remission of disease⁶⁹. Cumulative toxicities include bone marrow suppres-

sion, infertility, hemorrhagic cystitis, and the development of cancer^{35, 67}. Cyclophosphamide is thus reserved for situations where other alternative options have failed or are contraindicated. It is a Category D drug (Table 2).

Chlorambucil. Chlorambucil has a similar mechanism of action to cyclophosphamide. In the uveitis and ocular immunology clinic it is generally reserved for severe therapy-resistant uveitis and systemic autoimmune diseases with vision-threatening uveitis. Chlorambucil is dosed orally from 0.1–0.2 mg/kg/day. Its indications are relatively narrow because of its severe long-term toxicity, which includes amenorrhea, irreversible azoospermia, and cumulative dose-related risk of malignancies, the risks of which increase with the dose administered^{13, 24, 26, 46}. The most common malignancies are hematological, which occurred in a range of 1.25–7.5% of juvenile idiopathic arthritis patients (juvenile rheumatoid) treated⁴⁶. These malignancies can occur years after the cessation of the use of the drug and thus long-term follow-up of patients for routine surveillance is essential⁴⁶. It is designated as a Category D drug by the FDA (Table 2).

Calcineurin inhibitors

Cyclosporine (CSA). CSA is a common first choice of a corticosteroid-sparing agent for patients with ocular inflammatory disease who require long-term immunosuppression, especially in those with co-existing macular edema^{26, 57}. The mechanism of action of CSA and tacrolimus involves inhibiting a common cytoplasmic target, calcineurin, associated with a subsequent decrease in interleukin (IL)-2, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ . It is available as oral capsules or in suspension form and initiated at 2 mg/kg/day, given in divided doses twice daily escalated over weeks in small increments to reach 3–5 mg/kg/day depending on the response and absence of adverse effects. In our experience, administering more than 5 mg/kg/day may be associated with nephrotoxicity. Different brands of the same dose of CSA are neither equivalent nor interchangeable, as the microemulsion may be 20–50% more bioavailable^{1, 31, 42}.

CSA is a calcineurin inhibitor which blocks the production of several cytokines, including IL-2, IL-3, and IL-4, by interfering with the IL-2 receptor (IL-2R; CD25), thus preventing the activation of T cells^{57, 70}. In comparison with the cytotoxic drugs mentioned above, CSA has a more specific effect on the immune system, predominantly inhibiting T lymphocytes. In combination with corticosteroids, CSA prevents and treats ongoing acute inflammation.

CSA is not dialyzable, is highly protein bound (90%), and can be passed to the infant via breast-feeding. Absorption of oral CSA is variable, with about 20–30% bioavailability and maximal peak concentration from 4–6 h after the dose.

Nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, hyperuricemia, headache, tremors, leg cramps, convulsions, hirsutism and acne, nausea/vomiting, abdominal pain, diarrhea, and gingival hyperplasia have all been reported in various studies^{1, 37, 38, 46, 57}. Multiple drug interactions can occur with CSA⁴³, thus physicians should review patients' current therapeutic regimens prior to prescribing. Diet is well known to interfere with its metabolism^{25, 52}. Grapefruit juice can increase the serum levels of CSA and certain herbal supplements such as St. Johns wort have been demonstrated to decrease CSA levels^{9, 25}.

Tacrolimus. Tacrolimus is less commonly used as an immunosuppressive drug by ophthalmologists due to its toxicity and cost. Also known as FK-506, tacrolimus inhibits the action of calcineurin, reducing both T cell and B cell activity⁴. Tacrolimus binds to FK-506 binding protein 12 and forms a complex with calcineurin, calmodulin, and calcium, inhibiting the dephosphorylation of the nuclear factor of activated T cells. The dephosphorylated form of the nuclear factor normally crosses the nuclear membrane and stimulates transcription of the IL-2 gene. Tacrolimus prevents the dephosphorylation of NF-AT and thus inhibits subsequent steps in this arm of the inflammatory cascade, reducing T cell activation and possibly inhibiting IgE production from B cells^{54, 62, 65}.

Its other mechanisms of action are related to mast cell stabilization as well as down-regulation of the expression of IgE receptors on Langerhans cells, one of the antigen-presenting cells that activate T cells⁵⁷. One of the more common uses of tacrolimus in uveitis is in the prevention of corneal graft rejection when an underlying autoimmune disease is the basis of the original pathological process. However, there are also reports of satisfactory results in posterior uveitis⁶⁵. The typical daily dose of tacrolimus at the National Eye Institute (NEI) is 0.03–0.10 mg/kg/day given in divided doses twice daily^{54, 62}. Tremor, headache, diarrhea, hypertension, nausea, liver enzyme elevations, and renal dysfunction are the most common adverse events reported, but these are data principally derived from transplant patients^{40, 57}.

Target of rapamycin inhibitors

Sirolimus. Sirolimus is a newer immunosuppressive agent which is currently undergoing pilot trials at the

NEI at a dose of 6 mg as a loading dose and 2 mg every other day orally with the aim of inducing tolerance⁵⁷ in patients with ocular inflammatory disease. The mechanism of action of sirolimus is distinct from that of CSA and tacrolimus, which are calcineurin inhibitors⁵⁵. Sirolimus and tacrolimus share the same intracellular target, namely the FKBP12 protein. Calcineurin inhibitors block the first phase of T cell activation by an interruption of the signal from the T cell receptor by blocking calcineurin, a serine-threonine phosphatase required for transcriptional activation of the IL-2 gene in response to T cell antigen receptor engagement. This decreases IL-2 production and subsequent T cell stimulation. Sirolimus interferes with the second phase of T cell activation. It interrupts the signal from the IL-2R and the receptors for other cytokines and growth factors. It blocks the signal transduction pathway required for the progression of cytokine-stimulated T cells from the G1 into the S phase, thus suppressing T cell proliferation driven by IL-2⁵⁵. However, it remains to be seen if inherent redundancy in the cytokine pathways would prove a problem in extended use in the therapy of ocular inflammation.

Purine synthesis inhibitors

Mycophenolate mofetil (MMF). Although MMF has similarities to AZT, inherent differences prompted classifying it as a selective purine synthesis inhibitor. MMF is a morpholinoethyl ester derivative of mycophenolic acid (MPA) which inhibits purine synthesis of human lymphocytes and thus, indirectly, T cell proliferation⁴⁵.

MMF is a more specific inhibitor than AZT. AZT inhibits IMP dehydrogenase as well as 5-phosphoribosyl-1-pyrophosphate (PRPP)-amidotransferase and adenylosuccinate synthetase^{5, 22, 73}. Because of the guanosine depletion and lack of activation of PRPP, mycophenolate mofetil may cause a non-specific inhibition of purine synthesis. However, they share a similar adverse effect profile and hence must not be combined⁴⁵. MMF is hydrolyzed to MPA in the liver and GI tract. The mofetil ester is almost entirely converted to the acid form, because there is little detected in the blood. The mofetil ester has significantly higher bioavailability than the acid form^{6, 72, 73}. In healthy volunteers the absorption was 94%. Food does not alter the extent of absorption, but the maximum concentration is decreased about 40%. MMF levels are affected by significant drug interactions with cholesterol binding resins and antacids (decrease) and with acyclovir (increase)^{6, 72, 73}. MMF is of great utility in the treatment of a wide variety of

ocular inflammatory diseases. The recommended starting dose is 500 mg twice daily (15 mg/kg/day in divided doses) and escalates to a maximum of 1000 mg twice daily over a month. Using data without appropriate statistical analysis, it appears that MMF has been probably associated with less adverse events such as significant leucopenia in the NEI clinic compared with reports on renal patients receiving 3 g daily^{45, 72, 73}. MMF is Pregnancy Category C (Table 2).

Biologics

Anti-TNF- α antibodies. Recently, several biologic agents have become available for treatment of autoimmune diseases such as Crohn's disease, Behcet's syndrome, rheumatoid arthritis, psoriasis, and uveitis. Of these biologics, TNF- α has emerged as being of major pathological significance, and therapy directed against TNF has already shown efficacy in ocular inflammatory conditions^{24, 26}. TNF is obligatory for chronic autoimmune diseases (although there may be exceptions¹⁷) and its existence provides a rationale for further studies into TNF-independent cytokine pathways, since ocular inflammatory cells express TNF- α ⁷⁶. Anti-TNF therapy has been associated with reactivation of chronic indolent infections such as tuberculosis (TB) and paradoxically increased autoimmune disease activity^{8, 39}. In one report from Spain the incidence of TB associated with infliximab (84% of patients were given infliximab) and etanercept (16%) in patients with rheumatoid arthritis was 1893 per 100,000 in the year 2000, prior to the establishment of TB prevention guidelines. After the guidelines were established there was a dramatic decline in TB incidence; only one case was reported in the first 5 months since implementation. Local urticarial reactions and headaches remain the most common and consistent adverse reaction in patients taking these agents. The urticarial reactions tend to diminish on repeated dosing^{66, 70}, but anaphylactic reactions compel discontinuation of this class of agents. Since demyelinating events have been reported as adverse effects of anti-TNF agents, patients must be evaluated for neurological conditions prior to initiation of therapy^{30, 70}.

Infliximab. Infliximab is a chimeric anti-TNF- α monoclonal antibody with high affinity and binding specificity for human TNF. Results from several controlled clinical trials show that repeated infusions of infliximab with or without concomitant MTX treatment can reduce the signs and symptoms of inflammatory diseases of the eye^{3, 8, 51, 66}. It is typically administered intravenously at 2-5 mg/kg every four weeks for non-infectious uveitic diseases, with the length of treatment dictated by the clinical response.

Etanercept. Etanercept, another TNF- α inhibitor, is less widely used than infliximab due to less therapeutic efficacy as well as possible immunogenicity of the drug itself^{8, 53}. The “unnatural” construct of the drug may have bearing on its propensity to be immunogenic^{20, 39}. However, the drug is still currently being used in the US for conditions such as rheumatoid arthritis at 0.3–0.4 mg/kg twice a week.

Anti-IL-2R antibody. Daclizumab is a murine-human chimerized monoclonal antibody against the IL-2R α receptor of T cells. It is FDA approved to prevent rejection in kidney transplants. Chimerization or “humanization” by incorporating the variable component with the constant portion of human IgG resulted in a subsequent increase in circulatory half-life and the elimination of clinically significant antibody response⁷⁰. Thus, daclizumab maintains its effectiveness on re-administration³⁸.

Daclizumab is given at 2 mg/kg intravenously once every four weeks in the kidney transplant patient. In the NEI trials, this dose has been demonstrated to reduce the incidence and severity of acute rejection in uveitis patients without significantly increasing the incidence of opportunistic infections or other adverse effects compared with placebo^{50, 56}.

Early reports from the NEI trials suggest that daclizumab can also be used as alternative therapy for a wide variety of autoimmune uveitis^{38, 57}. There have been no reports to date of anaphylactic reactions or antibody production^{50, 70}. The total T cell population remains in the normal range in patients on daclizumab as the drug preferentially targets activated T cells that are CD25⁺. This suggests that in addition to competitive binding and saturating the CD25 receptor, down-regulation of IL-2R expression, shedding of antibody-bound IL-2R, or destruction of activated T cells by antibody-driven pathways may play a role in the mechanism of action⁵⁰. Longer follow-up studies are needed to evaluate its toxicities.

Anti-CD20 antibody. Rituximab is the first monoclonal antibody approved for the treatment of relapsed or refractory low-grade or follicular, CD20⁺, B cell non-Hodgkin's lymphomas in the United States. The role of B cells in the T cell-mediated conditions is being studied, and reports suggest possible benefits in targeting B cells in certain ocular inflammatory conditions³³.

IFN- α . This biological agent has shown promise in treatment of certain conditions such as Behcet's disease, but is yet to get to the mainstream of current therapeutic choices⁴¹. The dosage is tailored for the

patient and clinical presentation. Adverse effects include retinopathy, which has been sporadically reported⁷⁹.

Miscellaneous

Thalidomide. Thalidomide is currently approved by the FDA for cautious use in Hansen's disease (earlier known as leprosy). However, its utility in the management of Behcet's disease is well documented^{32, 57}. Besides its ability to cause drowsiness and birth deformities, it may also cause a potentially irreversible peripheral neuropathy. However, its unique immunomodulating properties are of interest in the management of autoimmune disorders (e.g. ulcers in Behcet's disease) that may be of functional or cosmetic concern⁵⁸ and perhaps may be extended in the near future to other autoimmune diseases.

Colchicine. Colchicine at an oral dose of 0.6 mg twice daily has been shown to be effective in the treatment of mucocutaneous ulcers associated with Behcet's disease⁵⁷. These ulcers can be very debilitating to patients. Colchicine's therapeutic effect is thought to be due to its inhibiting the formation of microtubules⁷⁸. It can cause gastric irritation, which may be a dose-dependent adverse effect.

Anti-infectious agents: acyclovir, foscarnet, and gancyclovir, sulpha drugs

Retinal diseases caused by herpetic viruses fall within the purveyance of the uveitis specialist. Acute retinal necrosis is a clinical diagnosis and usually results from herpetic infection; however, cytomegalovirus (CMV) infection and toxoplasmosis may present similarly^{11, 57}. The clinical examination, including the evolutionary and drug history, usually helps distinguish the condition. If the patient is severely immunosuppressed (bone marrow transplant, AIDS, or extensive myeloablative radiation and low CD4 counts <50), CMV retinitis must be included in the differential, and gancyclovir and/or foscarnet initiated empirically. Both of these drugs also treat herpetic viruses. The location of the lesion and the threat to macula as well as the degree of immunocompromise would dictate the use of intravitreal antivirals. Most ocular viral diseases are dormant; therefore, long-term suppressive medication may be required. In patients with AIDS, progressive outer-retinal necrosis (PORN) is another entity where the degree of intraocular inflammatory response may be much less than the retinal lesions that suggest a typical vessel-sparing pattern. Typically, herpetic viruses are associated with PORN and management of PORN requires frequent intravitreal medications over a pro-

longed period of time until the blood T cell count rises to an acceptable level as determined in conjunction with an infectious disease expert. For CMV retinitis, a long-acting gancyclovir implant is available which may improve the quality of the patient's life as well as achieve sustainable levels of the drug in the eye. If the diagnosis is uncertain, speedy referral must be done to a uveitis or retinal specialist. Barrier laser therapy may be required to seal off the necrotic retina, and sometimes 360° laser retinopexy is performed prophylactically. Similarly, antivirals, such as topical trifluridine (at least 9 times daily), have been demonstrated to speed the treatment for herpetic corneal lesions. Acyclovir is designated as a Pregnancy Category B drug by the FDA. All the antivirals are only virostatic.

Toxoplasmosis is the leading cause of posterior uveitis in the immunocompetent adult and it potentially leads to blindness in certain endemic countries such as Brazil, France, and the USA. Ocular toxoplasmosis can be a recurrence of a congenital infection or newly acquired⁶⁴. In immunodeficient patients, particularly AIDS patients, it can have both systemic lesions in the brain and atypical lesions in the eye. Typical ocular findings include satellite, necrotizing retinitis adjacent to an existing chorioretinal scar accompanied by dense vitritis. Ocular toxoplasmosis can present in other forms, such as anterior uveitis, pars-planitis, scleritis, and papillitis. In immunocompetent patients, ocular toxoplasmosis presents as an intraocular inflammation highlighted with vitritis at the border of a typical hyperpigmented scar⁵⁷. Antibodies against toxoplasmosis are not protective, and the disease can reactivate multiple times.

Sulpha drugs are used in the therapy of ocular disease and the initial drugs of choice remain sulphadiazine in a 2–4 g oral single loading dose, followed by oral 1 g four times daily and pyrimethamine 50 mg twice daily then 25 mg twice daily^{63, 64}. When prednisone is added to quell the inflammatory component of the disease, it comprises a “triple therapy” for ocular toxoplasmosis. At the NEI, prednisone is added two days after initiating the antimicrobials. A well-designed trial has shown benefits in continuing the sulpha drugs for a year as prophylaxis, but the adverse events associated with the drug must also be taken into account if a lengthy course of therapy is planned^{61, 63, 64}. Alternative drugs used are clindamycin 300 mg orally four times daily and 800 mg of sulfamethoxazole combined with 160 mg of trimethoprim (double-strength Bactrim: sulpha drug) twice daily. All of the above anti-toxoplasmosis drug choices aside from steroids are FDA Category C drugs, but

clearly the benefit of use should outweigh the risk in pregnant women.

Topical therapy

Corticosteroid injections. Periocular corticosteroids are frequently used in the therapy of uveitis without active systemic diseases. Triamcinolone 1% suspension is the drug of choice and the therapeutic effect appears to last for an average of 3–6 weeks. Complications of injections include accidental injury to the globe, secondary prolonged elevation in intraocular pressures, and cataract formation. Severe complications of surgical procedures include infection and retrobulbar hemorrhage. Primary open-angle glaucoma is an absolute contraindication for this procedure. Another route is intravitreal injection. The same complications may develop on a higher scale. The drug effect lasts for up to three months^{29, 57}. A vitreous biopsy or aqueous aspiration is useful for the diagnosis of microorganisms¹⁹.

MTX has been used as an adjunct for relapsed primary intraocular lymphoma in selected patients at the NEI with some degree of success. Since CNS lymphoma is a systemic malignancy, systemic treatment is the general approach. However, the quality of life may be improved with intravitreal MTX in patients with solely ocular disease. The therapeutic dose used at the NEI is 400 µg delivered intravitreally and continued depending on the response to therapy²³.

SURGICAL APPROACHES: DIAGNOSTIC AND THERAPEUTIC

Diagnosis

Surgery in patients with uveitis is fraught with complications even when the surgical techniques are performed flawlessly, because even meticulous surgery has the propensity to exacerbate inflammation^{24, 44, 57, 59}. However, aqueous taps with a 27 or 30 gauge needle are relatively safe in expert hands. If the aqueous humor is plasmoid, a wider-bore needle should be used to avoid chamber collapse and lens injury.

Vitreous taps for diagnostic purposes (endophthalmitis¹⁴, lymphoma or other malignancies¹⁸) can be performed in a similar manner to aqueous taps in synergetic eyes by a surgeon experienced in such conditions. In younger patients a standard vitrectomy is more advisable. Before attempting a biopsy it is imperative to discuss the case and have the ocular pathologist examine the patient and instruct the appropriate method for tissue handling. For example, prompt transport and processing of biopsied ocu-

lar samples is critical for a successful diagnosis of primary intraocular lymphoma¹⁸. In the case of vitreous or chorioretinal biopsies it is imperative that corticosteroid or immunosuppressive agents that may affect or modify the sample quality (number of viable lymphoma cells) or harm the eye (suspected infections) be judiciously avoided pre-operatively. In the case of lymphoma, the eye is generally quiet and non-inflamed, but in endophthalmitis the clinical picture leads to the diagnosis in most cases⁵⁷.

Treatment

Cataract extractions are often required in patients with uveitis because of inflammation and long-term use of therapeutic corticosteroids. In children there is also a constant risk of amblyopia prompting early intervention. Such surgeries are electively timed at the NEI after documentation of an arbitrary 3-month absence of intraocular inflammation on or off medications. It is paramount that intraocular inflammation be well controlled prior to surgery⁵⁷. Immunosuppressive therapy should be added pre- and post-surgery and carefully tapered off on a case by case basis^{38, 49, 57}. Intraocular lenses are placed depending on each case. In general, a patient with a history of severe inflammatory recurrences would not be considered a good candidate^{49, 59}. Similarly, any posterior segment surgery should be managed in the manner mentioned above with the caveat that post-surgical proliferative vitreoretinopathy may occur in spite of excellent immediate post-operative results. The incidence of pthysical changes postoperatively is more likely in a uveitic eye and more so if critical post-operative management is sub-optimal. Consultation with a uveitis specialist is recommended while planning surgery in such patients to ensure good results^{24, 37, 44, 57, 59}. The surgeon must be aware that surgery by itself cannot be “curative” or even therapeutic for systemic diseases.

NEW MODALITIES AND EXPERIMENTAL APPROACHES

Stem cell transplant

Autologous hematopoietic stem cell transplantation has been proposed as a potential treatment for autoimmune disease^{10, 16}. Prolonged remission of autoimmune disease has been observed in patients who undergo allogeneic and, more recently, autologous bone marrow transplant for hematopoietic or other malignancy⁶⁰. Evidence from disease-susceptible strains of animals show that autologous hematopoietic stem cells may help cure autoimmune disease possibly by inducing tolerance to the inciting agent. Immunosuppressive treatments with higher

dose regimens (and toxicities) combined with some form of bone marrow “rescue” may be an alternative to standard care in cases refractory to conventional therapy^{10, 15, 16}.

Macrobiomolecules

Macrobiomolecules are a topic of current research in biomedical sciences as they represent a relatively nontoxic method of creating “designer drugs” with potential application for ocular inflammatory disease affecting the ocular surface (rosacea and dry eyes)⁷¹. It is likely that there will be broadening of the application of these molecules in ocular inflammatory disease.

Plasmapheresis

Plasmapheresis is a useful tool rarely used that can temporize patients with paraproteinemia-associated retinopathy until definitive treatment is initiated.

Intravenous immunoglobulin

Intravenous immunoglobulin with steroids may possibly be useful in retinal vasculitis associated with conditions such as Kawasaki’s disease as it appears to help vasculitis in other organs²¹.

FUTURE DEVELOPMENTS

It is likely that pharmacogenomics will play a more important role in the choice of our therapeutic options individualized to the patient’s gene polymorphisms or RNA-expression profiles⁴⁷. It may be then possible to tailor the type of drug and dosage based on this type of data. Genomic profiles are already being increasingly used in cancer patients to predict the course of the response to existing therapy. There will be more relatively nontoxic drugs available in the armamentarium of uveitis specialists, as the market for these drugs is primarily driven by rheumatologic diseases and transplantations, both of which will grow even more as the population ages^{76, 77}.

CONCLUSION

Non-infectious inflammation in the eye is usually considered an autoimmune disease and requires anti-inflammatory agents to modulate local and/or systemic immune system responses. The rationale for therapy, as in any other condition, must be carefully considered before a decision is made. Most immunosuppressive agents have significant adverse effects. Patients on these drugs must be considered immunosuppressed even at lower doses, and any intercurrent

illness during therapy warrants a workup to exclude an adverse drug reaction and secondary opportunistic infections or malignancies. Patients on immunosuppressive therapy should be warned about the possibility of certain vaccines being ineffective and the danger of live vaccines potentially causing the very infections they was designed to prevent⁷⁰. When dealing with patients of childbearing age it is mandatory to inform the patient of the potent adverse reproductive effects of the drugs used and obtain adequate consultation. If there is an inadvertent exposure in utero to toxic agents, fetal medicine should be informed and a notation made in the chart to avoid repeating the error.

Therapy should be directed objectively at reducing inflammatory signs quantified as erythema, cells and flare in the anterior chamber, cells and haze in the vitreous humor, as well as lesions in the uvea and retina. Vision may serve as an indicator of response to therapy, particularly when macular edema develops. Often the eye can be a sign of systemic disease; therefore, systemic examination and consultations by other specialists are required. Some patients have been demonstrated to mount a paradoxically increased immune response with certain therapeutic drugs used in the practice of uveitis. Examples of this phenomenon are uveitis associated with etanercept use^{39, 53} or anti-TNF agents in general⁵³, pulmonary toxicity associated with cyclophosphamide³⁵, and the described *in vitro* chemotactic properties of cyclopentolate⁵⁷.

Unilaterality and absence of systemic disease would argue for a more localized intervention, such as pericocular injections. The age, sex, and clinical history of previous therapy, whether successful or failed,

must be included in the decision-making process. Both the therapy and its goals must be tailored to the patient and the condition. It cannot be overstated that infections, especially viral or mycobacterial, may simulate autoimmune diseases of the eye^{11, 14, 34, 75}. Here, immunosuppression would lead to disastrous consequences. Appropriate testing (e.g. vitreous tap in suspected infections) or referral to more experienced surgeons should be considered at the outset. Similarly, immunosuppressives may mask malignancies presenting in the eye, confound the diagnostic tests, and complicate systemic therapy that is often required⁵⁷. There are clear associations between certain drugs and intraocular inflammation such as cytarabine, rifabutin and anterior uveitis or latanoprost and macular edema⁵⁷. A foreign body in the eye can also present as chronic or acute intraocular inflammation⁵⁷. Here, a good clinical history helps the physician avoid unnecessary diagnostic and therapeutic interventions.

It is vital that ophthalmologists and other related physicians be aware of the increasing array of immunosuppressive medications available to patients today. This review has been a guide to help readers understand the pharmacology and philosophy behind some of those therapeutic modalities. We strongly encourage interested readers to study the original references and broaden their knowledge of ongoing developments in the field.

ACKNOWLEDGMENT

The authors would like to thank Kenny Lim, M.D., for reviewing and editing the manuscript.

REFERENCES

- (2003): Gengraf (cyclosporine capsules). In: Prescribing information. Abbott Lab.
- (2004–2005): Section 9: Intraocular inflammation and uveitis. In Opremac E. M. (ed.): Basic and Clinical Science Course (BCSC). Foundation of the American Academy of Ophthalmology, San Francisco.
- Aeberli D., Oertle S., Mauron H., Reichenbach S., Jordi B. and Villiger P. M. (2002): Inhibition of the TNF-pathway: use of infliximab and etanercept as remission-inducing agents in cases of therapy-resistant chronic inflammatory disorders. *Swiss Med. Wkly.*, 132, 414–422.
- Afshari N. A., Afshari M. A. and Foster C. S. (2001): Inflammatory conditions of the eye associated with rheumatic diseases. *Curr. Rheumatol. Rep.*, 3, 453–458.
- Allison A. C. and Eugui E. M. (1993): Immunosuppressive and other effects of mycophenolic acid and an ester prodrug, mycophenolate mofetil. *Immunol. Rev.*, 136, 5–28.
- Allison A. C. and Eugui E. M. (2000): Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology*, 47, 85–118.
- Araujo A. A., Wells A. P., Dick A. D. and Forrester J. V. (2000): Early treatment with cyclosporin in serpiginous choroidopathy maintains remission and good visual outcome. *Br. J. Ophthalmol.*, 84, 979–982.
- Baert F., Noman M., Vermeire S., Van Assche G., D'Haens G., Carbonez A. and Rutgeerts P. (2003): Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N. Engl. J. Med.*, 348, 601–608.
- Bauer S., Stormer E., John A., Kruger H., Budde K., Neumayer H. H., Roots I. and Mai I. (2003): Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br. J. Clin. Pharmacol.*, 55, 203–211.
- Binks M., Passweg J. R., Furst D., McSweeney P., Sullivan K., Besenthal C., Finke J., Peter H. H., van Laar J., Breedveld F. C., Fibbe W. E., Farge D., Gluckman E., Locatelli F., Martini A., van den Hoogen F., van de Putte L., Schattenberg A. V., Arnold R., Bacon P. A., Emery P., Espigado I., Hertenstein B., Hiepe F., Kashyap A., Kotter I., Marmont A., Martinez A., Pascual M. J., Gratwohl A., Prentice H. G., Black C. and Tyndall A. (2001): Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. *Ann. Rheum. Dis.*, 60, 577–584.

11. Bodaghi B., Rozenberg F., Cassoux N., Fardeau C. and LeHoang P. (2003): Nonnecrotizing herpetic retinopathies masquerading as severe posterior uveitis. *Ophthalmology*, 110, 1737–1743.
12. Boumpas D. T., Chrousos G. P., Wilder R. L., Cupps T. R. and Balow J. E. (1993): Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann. Intern. Med.*, 119, 1198–1208.
13. Brogan P. A. and Dillon M. J. (2000): The use of immunosuppressive and cytotoxic drugs in non-malignant disease. *Arch. Dis. Child*, 83, 259–264.
14. Buggage R. R., Callanan D. G., Shen D. F. and Chan C. C. (2003): *Propionibacterium acnes* endophthalmitis diagnosed by microdissection and PCR. *Br. J. Ophthalmol.*, 87, 1190–1191.
15. Burt R. K., Kallunian K., Patel D., Thomas J., Yeager A., Traynor A., Heipe F., Arnold R., Marmont A., Collier D., Glatstein E. and Snowden J. (2004): The rationale behind autologous autoimmune hematopoietic stem cell transplant conditioning regimens: concerns over the use of total-body irradiation in systemic sclerosis. *Bone Marrow Transplant.*, 34, 745–751.
16. Burt R. K. and Traynor A. E. (1999): Hematopoietic stem cell transplantation: a new therapy for autoimmune disease. *Oncologist*, 4, 77–83.
17. Campbell I. K., O'Donnell K., Lawlor K. E. and Wicks I. P. (2001): Severe inflammatory arthritis and lymphadenopathy in the absence of TNF. *J. Clin. Invest.*, 107, 1519–1527.
18. Chan C. C., Buggage R. R. and Nussenblatt R. B. (2002): Intraocular lymphoma. *Curr. Opin. Ophthalmol.*, 13, 4110–418.
19. Chan C. C., Palestine A. G., Li Q. and Nussenblatt R. B. (1994): Diagnosis of ocular toxoplasmosis by the use of immunocytology and the polymerase chain reaction. *Am. J. Ophthalmol.*, 117, 803–805.
20. Christopher-Stine L. and Wigley F. (2003): Tumor necrosis factor- α antagonists induce lupus-like syndrome in patients with scleroderma overlap/mixed connective tissue disease. *J. Rheumatol.*, 30, 2725–2727.
21. Cimaz R. and Falcini F. (2003): An update on Kawasaki disease. *Autoimmun. Rev.*, 2, 258–263.
22. Cuffari C., Hunt S. and Bayless T. (2001): Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut*, 48, 642–646.
23. de Smet M. D., Vancs V. S., Kohler D., Solomon D. and Chan C. C. (1999): Intravitreal hemotherapy for the treatment of recurrent intraocular lymphoma. *Br. J. Ophthalmol.*, 83, 448–451.
24. Djalilian A. R. and Nussenblatt R. B. (2002): Immunosuppression in uveitis. *Ophthalmol. Clin. North Am.*, 15, 395–404.
25. Dresser G. K. and Bailey D. G. (2003): The effects of fruit juices on drug disposition: a new model for drug interactions. *Eur. J. Clin. Invest.*, 33 (suppl. 2), 10–16.
26. Dunn J. P. (2004): Review of immunosuppressive drug therapy in uveitis. *Curr. Opin. Ophthalmol.*, 15, 293–298.
27. El-Azhary R. A. (2003): Azathioprine: current status and future considerations. *Int. J. Dermatol.*, 42, 335–341.
28. FDA U.S. (2000): FDA oncology tools product label details in conventional order for methotrexate. In Product label. Center for drug evaluation and research. Food and Drug Administration, Rockville.
29. Gillies M. C., Simpson J. M., Luo W., Penfold P., Hunyor A. B., Chua W., Mitchell P. and Billson F. (2003): A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. *Arch. Ophthalmol.*, 121, 667–673.
30. Gordon L. K. (2004): Uveitis and neurological diseases. *Br. J. Ophthalmol.*, 88, 1483–1484.
31. Halloran P. F. (2004): Immunosuppressive drugs for kidney transplantation. *N. Engl. J. Med.*, 351, 2715–2729.
32. Hamuryudan V., Mat C., Saip S., Ozyazgan Y., Siva A., Yurdakul S., S Zwingenberger S. and Yazici H. (1998): Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.*, 128, 443–450.
33. Hayashi T., Hideshima T., Akiyama M., Podar K., Yasui H., Raje N., Kumar S., Chauhan D., Treon S. P., Richardson P. and Anderson K. C. (2005): Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. *Br. J. Haematol.*, 128, 192–203.
34. Hollander D. A., Dodds E. M., Rossetti S. B., Wood I. S. and Alvarado J. A. (2004): *Propionibacterium acnes* endophthalmitis with bacterial sequestration in a Molteno's implant after cataract extraction. *Am. J. Ophthalmol.*, 138, 878–879.
35. Hoover R. and Fraumeni J. F. Jr. (1981): Drug-induced cancer. *Cancer*, 47, 1071–1080.
36. Hows J. M., Mehta A., Ward L., Woods K., Perez R., Gordon M. Y. and Gordon-Smith E. C. (1984): Comparison of mesna with forced diuresis to prevent cyclophosphamide induced haemorrhagic cystitis in marrow transplantation: a prospective randomised study. *Br. J. Cancer*, 50, 753–756.
37. Jabs D. A. (2004): Treatment of ocular inflammation. *Ocul. Immunol. Inflamm.*, 12, 163–168.
38. Jabs D. A., Rosenbaum J. T., Foster C. S., Holland G. N., Jaffe G. J., Louie J. S., Nussenblatt R. B., Stiehm E. R., Tessler H., Van Gelder R. N., Whitcup S. M. and Yocum D. (2000): Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am. J. Ophthalmol.*, 130, 492–513.
39. Kaipiainen-Seppanen O. and Leino M. (2003): Recurrent uveitis in a patient with juvenile spondyloarthritis associated with tumour necrosis factor α inhibitors. *Ann. Rheum. Dis.*, 62, 88–89.
40. Kershner R. P. and Fitzsimmons W. E. (1996): Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. *Transplantation*, 62, 920–926.
41. Kotter I., Gunaydin I., Treusch M., Zierhut M., Kanz L. and Stubiger N. (2003): The use of interferon- α in Behcet's disease – review of the literature and possible mechanisms of action. *Adv. Exp. Med. Biol.*, 528, 503–509.
42. Koyama S., Takamizawa A., Sato E., Masubuchi T., Nagai S. and Izumi T. (2001): Cyclophosphamide stimulates lung fibroblasts to release neutrophil and monocyte chemoattractants. *Am. J. Physiol. Lung Cell. Mol. Physiol.*, 280, L1203–L1211.
43. Krieger N. R. and Emre S. (2004): Novel immunosuppressants. *Pediatr. Transplant.*, 8, 594–599.
44. Lam L. A., Lowder C. Y., Baerveldt G., Smith S. D. and Traboulsi E. I. (2003): Surgical management of cataracts in children with juvenile rheumatoid arthritis-associated uveitis. *Am. J. Ophthalmol.*, 135, 772–778.
45. Larkin G. and Lightman S. (1999): Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. *Ophthalmology*, 106, 370–374.
46. Laxer R. M. (1999): Long-term toxicity of immune suppression in juvenile rheumatic diseases. *Rheumatology*, 38, 743–746.
47. Lee W. M. (2003): Drug-induced hepatotoxicity. *N. Engl. J. Med.*, 349, 474–485.
48. Leung D. Y. and Bloom J. W. (2003): Update on glucocorticoid action and resistance. *J. Allergy Clin. Immunol.*, 111, 3–22.
49. Lightman S. and Kok H. (2002): Developments in the treatment of uveitis. *Expert Opin. Investig. Drugs*, 11, 59–67.
50. Maes B. D. and Vanrenterghem Y. F. (1999): Anti-interleukin-2 receptor monoclonal antibodies in renal transplantation. *Nephrol. Dial. Transplant.*, 14, 2824–2826.
51. Markomichelakis N. N., Theodossiadis P. G., Pantelia E., Papaefthymiou S., Theodossiadis G. P. and Sfrikakis P. P. (2004): Infliximab for chronic cystoid macular edema associated with uveitis. *Am. J. Ophthalmol.*, 138, 648–650.
52. Martin J. E., Daoud A. J., Schroeder T. J. and First M. R. (1999): The clinical and economic potential of cyclosporin drug interactions. *Pharmacoeconomics*, 15, 317–337.

53. Matzkies F. G., Manger B., Schmitt-Haendle M., Nagel T., Kraetsch H. G., Kalden J. R. and Schulze-Koops H. (2003): Severe septicaemia in a patient with polycondritis and Sweet's syndrome after initiation of treatment with infliximab. *Ann. Rheum. Dis.*, 62, 81–82.
54. Mochizuki M., Masuda K., Sakane T., Ito K., Kogure M., Sugino N., Usui M., Mizushima Y., Ohno S., Inaba G. et al. (1993): A clinical trial of FK506 in refractory uveitis. *Am. J. Ophthalmol.*, 115, 763–769.
55. Morelon E., Mamzer-Bruneel M. F., Peraldi M. N. and Kreis H. (2001): Sirolimus: a new promising immunosuppressive drug. Towards a rationale for its use in renal transplantation. *Nephrol. Dial. Transplant.*, 16, 18–20.
56. Nussenblatt R. B., Fortin E., Schiffman R., Rizzo L., Smith J., Van Veldhuisen P., Sran P., Yaffe A., Goldman C. K., Waldmann T. A. and Whitcup S. M. (1999): Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb: a phase I/II clinical trial. *Proc. Natl. Acad. Sci. USA*, 96, 7462–7466.
57. Nussenblatt R. B. and Whitczer S. (2003): *Uveitis: Fundamentals and Clinical Practice*. Mosby, St. Louis.
58. Perri A. J. 3rd. and Hsu S. (2003): A review of thalidomide's history and current dermatological applications. *Dermatol. Online J.*, 9, 5.
59. Rahman I. and Jones N. P. (2005): Long-term results of cataract extraction with intraocular lens implantation in patients with uveitis. *Eye*, 19, 191–197.
60. Rossi G., Moretta A. and Locatelli F. (2004): Autologous hematopoietic stem cell transplantation for severe/refractory intestinal Behcet disease. *Blood*, 103, 748–750.
61. Rothova A., Bosch-Driessen L. E., van Loon N. H. and Treffers W. F. (1998): Azithromycin for ocular toxoplasmosis. *Br. J. Ophthalmol.*, 82, 1306–1308.
62. Sakane T., Mochizuki M., Inaba G. and Masuda K. (1995): [A phase II study of FK506 (tacrolimus) on refractory uveitis associated with Behcet's disease and allied conditions]. *Ryumachi*, 35, 802–813.
63. Silveira C., Belfort R. Jr., Muccioli C., Holland G. N., Victora C. G., Horta B. L., Yu F. and Nussenblatt R. B. (2002): The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. *Am. J. Ophthalmol.*, 134, 41–46.
64. Silveira C., Ferreira R., Muccioli C., R. Nussenblatt R. and Belfort R. Jr. (2003). Toxoplasmosis transmitted to a newborn from the mother infected 20 years earlier. *Am. J. Ophthalmol.*, 136, 370–371.
65. Sloper C. M., Powell R. J. and Dua H. S. (1999): Tacrolimus (FK506) in the treatment of posterior uveitis refractory to cyclosporine. *Ophthalmology*, 106, 723–728.
66. Smith J. R., Levinson R. D., Holland G. N., Jabs D. A., Robinson M. R., Whitcup S. M. and Rosenbaum J. T. (2001): Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum.*, 45, 252–257.
67. Talar-Williams C., Hijazi Y. M., Walther M. M., Linehan W. M., Hallahan C. W., Lubensky I., Kerr G. S., Hoffman G. S., Fauci A. S. and Sneller M. C. (1996): Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann. Intern. Med.*, 124, 477–484.
68. Thelkeld D. S. (1997): *Adrenal cortical steroids. In drug facts and comparisons*. Mosby, St. Louis.
69. Tiede I., Fritz G., Strand S., Poppe D., Dvorsky R., Strand D., Lehr H. A., Wirtz S., Becker C., Atreya R., Mudter J., Hildner K., Bartsch B., Holtmann M., Blumberg R., Walczak H., Iven H., Galle P. R., Ahmadian M. R. and Neurath M. F. (2003): CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J. Clin. Invest.*, 111, 1133–1145.
70. Tsokos G. (2002): *Modern therapeutics in rheumatic diseases*. Humana Press, Totowa.
71. Tuo J. and Chan C. C. (2003): Ocular application of macrobiomolecules in anti-allergy and anti-inflammation. *Curr. Med. Chem.*, 2, 219.
72. Wang K., Zhang H., Li Y., Wei Q., Li H., Yang Y. and Lu Y. (2004): Efficacy of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. *Transplant. Proc.*, 36, 2071–2072.
73. Wang K., Zhang H., Li Y., Wei Q., Li H., Yang Y. and Lu Y. (2004): Safety of mycophenolate mofetil versus azathioprine in renal transplantation: a systematic review. *Transplant. Proc.*, 36, 2068–2070.
74. Wegrzyn J., Adeleine P. and Miossec P. (2004): Better efficacy of methotrexate given by intramuscular injection than orally in patients with rheumatoid arthritis. *Ann. Rheum. Dis.*, 63, 1232–1234.
75. Whitcup S. M., Belfort R. Jr., de Smet M. D., Palestine A. G., Nussenblatt R. B. and Chan C. C. (1991): Immunohistochemistry of the inflammatory response in *Propionibacterium acnes* endophthalmitis. *Arch. Ophthalmol.*, 109, 978–979.
76. Whitcup S. M., Chan C. C., Li Q. and Nussenblatt R. B. (1992): Expression of cell adhesion molecules in posterior uveitis. *Arch. Ophthalmol.*, 110, 662–666.
77. Whitcup S. M. and Nussenblatt R. B. (1993): Treatment of autoimmune uveitis. *Ann. NY Acad. Sci.*, 696, 307–318.
78. Wigley F. M. and Sule S. D. (2001): Novel therapy in the treatment of scleroderma. *Expert Opin. Investig. Drugs*, 10, 31–38.
79. Willson R. A. (2004): Visual side effects of pegylated interferon during therapy for chronic hepatitis C infection. *J. Clin. Gastroenterol.*, 38, 717–722.