

# Systemic medications effective in treating uveitis, but need careful monitoring

**Dermot McGrath  
in Monte Carlo**

SYSTEMIC corticosteroids and immunosuppressants are potent agents in the treatment of ocular inflammatory diseases with best results achieved when physicians adhere to proper dosing techniques, according to Douglas A. Jabs MD, Johns Hopkins University School of Medicine, Baltimore, Maryland, US.

Speaking at the 5th International Symposium on Ocular Pharmacology and Therapeutics (ISOPT), Dr Jabs said that while the use of such drugs has the potential for serious side effects, their undoubted efficacy provided an acceptable risk benefit profile for most patients with serious ocular inflammation.

Most common problems associated with taking oral corticosteroids such as sleeplessness, mood swings, cushingoid habitus and elevated intraocular pressure are reversible and typically resolve with dose reduction, said Dr Jabs.

Other side effects that must be monitored more carefully include weight gain, hypertension, fluid retention and osteoporosis. A third category of side effects, which includes ischaemic necrosis of bone, psychosis, osteoporosis and myopathy, have more adverse effects on patient health and mark the point of departure into immunosuppressive therapy, he said.

Oral corticosteroid therapy can be used reasonably safely in the intermediate term if you can administer them at low doses, but at high doses these type of side effects are unacceptable and require the addition of an immunosuppressive agent, said Dr Jabs.

"The initial dose of steroids I would typically recommend is in the range of 1.0 mg/kg/day but rarely above the 60 mg to 80

mg/day range. Once the disease is quiet the goal is really to get that target dose for chronic disease less than 10 mg a day," he said.

To illustrate the risks of doses of steroids above the 80 mg range, Dr Jabs presented data showing how ischaemic necrosis of bone increased depending on the amount of prednisone taken by patients.

"The recommendations to use doses of prednisone over 60 mg to 80 mg per day are inappropriate. If the dose is up over 60 mg, the necrosis starts to get high and up over 100 mg it becomes unacceptably high. The same is true when we look at the data for the first six months doses of prednisone and underlines why it is vital to get the dose of prednisone down below 10 mg/day within the first three months and try to keep it there," he said.

Osteoporosis is another known side effect of corticosteroids, even at low doses, and he recommended that ophthalmologists could lessen its impact by advising patients to exercise regularly and take calcium supplements. He also recommended that patients receive annual bone density screenings and be given a bisphosphonate if they are osteoporotic or osteopenic.

Reviewing the range of immunosuppressive agents currently in use, Dr Jabs said that they are very effective in treating inflammation but required careful monitoring and individualised treatments to obtain optimal results.

He explained that these immunosuppressive drugs broadly divided into three classes: anti-metabolites (azathioprine, methotrexate, mycophenolate.), T-cell inhibitors (cyclosporine, tacrolimus) and alkylating agents (cyclophosphamide, chlorambucil). While objective data on the efficacy of a lot of these drugs in ocu-

lar inflammatory disease remained elusive, some general trends were emerging in terms of known side effects of these therapies.

The anti-metabolite azathioprine, for example, had demonstrated its efficacy in randomised controlled trials and seemed to be relatively safe, said Dr Jabs. Known issues with the agent were gastrointestinal upset in about one-in-five patients as well as isolated incidences of liver function abnormalities and bone marrow suppression in about 1.0

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% of cases exposed to longer-term treatment.

Side effects of methotrexate, another corticosteroid sparing agent, include gastrointestinal upset, fatigue, hepatitis and psoriasis. In a large study at Massachusetts Eye and Ear Infirmary, methotrexate was stopped for side effects in about 20% of patients.

Substantial case series data was available on the use of T-cell inhibitor cyclosporine in diseases such as Behcet's and uveitis, noted Dr Jabs. Side effects to watch out for include hypertension, hirsutism and, in particular, nephrotoxicity.

Less data from controlled clinical trials were available for tacrolimus, but known toxicities associated with the drug include nephrotoxicity, gastrointestinal problems, hypertension, hepatitis, metabolic abnormalities and diabetes.

"Each of these side effects has been reported at somewhere between 15% and 40% in uncontrolled case series and they really have limited the use of tacrolimus

for the moment as an immunosuppressive drug for uveitis," he said.

Dr Jabs noted that alkylating agents are the most potent immunomodulatory drugs used in treatment of uveitis and could induce long-term drug-free remission if used appropriately. Their principal drawback was their side effects, which included bone marrow suppression, infection, sterility and an increased risk of malignancy.

Although acknowledging that

the risk of malignancy underscored the need for very careful monitoring of patients taking alkylating agents, he said that the risk benefit profile was nevertheless acceptable for most patients with serious ocular inflammation.

"With some diseases such as mucous membrane pemphigoid, an alkylating agent really can make a huge difference. When we put plainly to patients the relative risks and benefits of alkylating therapy for their condition, over 90% agree to the treatment because they value their vision much above the possible remote risk of malignancy. I think it is a testament to the value of vision in every patient that we see," he said.

The means of administering drugs also plays an important part in determining the type and severity of side effects associated with corticosteroid use, said William Ayliffe FRCS PhD, Croydon Eye Unit, Mayday University Hospital, Surrey, UK.

"There are almost as many ways of administering these drugs

as there are steroids themselves," said Dr Ayliffe.

He noted that regional injections of steroids were now being used in an attempt to deliver the drug to the posterior segment while avoiding complications associated with systemic delivery, but said that this assumption was not necessarily correct.

Intracameral injections were also becoming increasingly popular, not just for uveitis but also for the potential treatment of diabetic cystoid macular oedema and choroid neovascularisation.

Known side effects with topical steroids include cataracts, elevated IOP and glaucoma, said Dr Ayliffe. He said that while some physicians were now proposing "non-penetrating steroids" to avoid such complications, the reality was actually more complex.

"We have to bear in mind that while these drugs are non-penetrating in animal models which are not inflamed; if you administer it to a child with severe inflammation you might be surprised to find a significant incidence of raised IOP and glaucoma. A recent study from China highlighted showed this swap from inflammatory eye disease to glaucoma, which is not a good thing at all," he said.

Systemic side effects of corticosteroid use included an increased risk of infection (varicella, tuberculosis) gastrointestinal problems (peptic ulcer, candidiasis, pancreatitis), fluid balance problems, skin changes, metabolic disturbance, musculoskeletal problems and psychiatric disturbance, noted Dr Ayliffe.

"The aim of steroid therapy should be to minimise dosing duration by using steroid sparing strategies whenever possible. Maybe what we will be doing in the next few years is not using steroids as a first-line drug at all.