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Cyclosporin therapy for severe scleritis

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SUMMARY To ascertain the efficacy of systemic cyclosporin therapy in the management of scleritis we performed an open, uncontrolled study of the use of this drug in severe refractory disease. Five of seven patients whose disease had previously been poorly controlled with a combination of corticosteroids and immunosuppressive drugs responded to cyclosporin therapy (10 mg/kg/day). Systemic side effects occurred in all but one patient, with tremor, hirsutism, hypertension, and raised serum creatinine being common. Recurrence of disease activity on decreasing the dosage of cyclosporin was frequent. The results indicate that cyclosporin is a useful additional drug in the treatment of severe scleritis.

Scleritis is a severe, potentially sight threatening, inflammatory disease involving the ocular surface. Despite recent advances its treatment remains a difficult problem. Systemic immunosuppressive therapy with corticosteroids or immunosuppressive agents or both is usually required to control the disease.[1] Early therapeutic intervention is important to prevent ocular complications and to minimise the potential morbidity and mortality associated with underlying systemic disease.

Systemic corticosteroids in high dosage, either orally or in intravenous pulses, are widely accepted as an effective form of treatment in patients with severe scleritis.[2,3] But this treatment is often associated with unacceptable side effects and does not always control scleral inflammation. The addition of immunosuppressive agents in patients with severe scleritis improves the ocular outcome and decreases the morbidity associated with systemically administered corticosteroids.[4] Azathioprine, cyclophosphamide, and cyclosporin have previously been reported to be effective and safe in the management of severe ocular inflammation.[2,5] We and others have reported the successful use of cyclosporin in the treatment of patients with a variety of ocular inflammatory syndromes resistent to other immunosuppressive regimens.[6,7] In the present study we report the therapeutic effect of cyclosporin in the treatment of severe scleritis.

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Patients and methods

Seven patients with scleritis were referred for assessment and treatment of their disease to the Ocular Immunology Clinic at St Vincent's Hospital. All seven patients were examined by the authors before and during their treatment and were followed up at regular intervals. They were also assessed by an ophthalmologist and an immunologist. A detailed history was taken and physical examination performed as well as appropriate investigations to exclude the presence of an associated systemic disease. Prior to treatment all patients had active ocular disease and were receiving a variety of topical and systemic anti-inflammatory drugs. These had either failed to control the disease and/or were associated with unacceptable side effects.

All patients were started on cyclosporin 10 mg per kilogram body weight daily. After two to four weeks of therapy the dose of cyclosporin was incrementally decreased at one- to two-week intervals until a dose of 5 mg/kg or less was reached in each patient. Pulse methylprednisolone or oral steroids were continued at the current dose and other immunosuppressive agents were stopped. Pulse steroids were then

Table 1 *Clinical features of patients with scleritis*

Patient age/sex	*Diagnosis*	*Duration (months)*	*Systemic association*	*Treatment complications prior to cyclosporin therapy*
1/44/F	Necrotising scleritis	6	Nil	Diabetes Anaemia
2/65/M	Necrotising scleritis	13	Nil	Diabetes Hypertension
3/58/F	Necrotising scleritis	24	Polyarteritis nodosa	Osteoporosis Cushingoid
4/48/F	Necrotising scleritis	19	Nil	Alopecia Leukopaenia
5/66/M	Necrotising scleritis	27	Nil	Diabetes
6/52/F	Necrotising scleritis	12	Nil	Nil
7/67/F	Necrotising scleritis	14	Nil	Cushingoid Hypertension

Duration was defined as the time from the onset of symptoms until cyclosporin therapy was begun.

Table 2 *Previous treatment*

Patient	*Drug*	*Dosage*	*Duration (months)*
1	Methylprednisolone	1 g-125 mg/dose	4
	Azathioprine	150 mg/day	3
2	Prednisolone	10-50 mg/day	2
	Methylprednisolone	1 g-250 mg/dose	5
	Cyclophosphamide	150 mg/day	3
3	Prednisolone	5-50 mg/day	3
	Methylprednisolone	1 g-250 mg/dose	4
	Azathioprine	150 mg/day	4
	Cyclophosphamide	150 mg/day	3
4	Prednisolone	0-50 mg/day	2
	Methylprednisolone	1 g-250 mg/dose	3
	Azathioprine	150 mg/day	2
	Cyclophosphamide	100 mg/day	3
5	Methylprednisolone	1 g-125 mg/dose	6
	Cyclophosphamide	100-200 mg/day	3·5
6	Prednisolone	0-100 mg/day	2
	Azathioprine	100-150 mg/day	2
7	Prednisolone	0-100 mg/day	14
	Methylprednisolone	1 g-125 mg/dose	4
	Aazthioprine	150 mg/day	4

Methylprednisolone was used as intermittent intravenous pulse therapy.

reduced according to our published protocol.[3] Treatment was initiated in several patients while they were in hospital for investigation and stabilisation of the disease.

A subjective grading system,[5] analogous to that previously described for patients with uveitis and retinal vasculitis was used. A scleritis score was calculated when the patients first presented and at each follow-up visit. Improvement was defined as a decrease in the total score of greater than 2 and resolution at a total score of less than or equal to 4.

Table 3 *Scoring system for severity of scleritis*

Clinical feature	*Clinical grading*	*Score*
1 Location	Unilateral	1
	Bilateral	3
2 Tenderness	0-4+	0-4
3 Nodules	Single	2
	Multiple	4
4 Scleral necrosis	Absent/quiescent	0
	Present	2
	Progressive	4
5 Visual acuity	Initially ≤6/18 or decrease by 2 or more lines	1
6 Anterior chamber cells	0-4+	0-4
7 Raised IOP	>22 mm Hg	1
8 Vitreous cells	0-4+	0-4
9 Retinal detachment	Absent	0
	Present	4

Improvement: a decrease in the scleritis score of 2 or more points.
Resolution: a decrease in the scleritis score to 4 or fewer points.
Each eye is scored separately. In bilateral disease the higher total score is used.
IOP=intraocular pressure.

Table 4 *Scleritis score in patients treated with cyclosporin*

Patient	*Pretreatment scleritis score*	*Scleritis score at three months*
1	12	4
2	10	9
3	12	3
4	9	3
5	13	13
6	10	3
7	12	3

Results

The clinical features of the patients are summarised in Table 1. There were five females with a mean age of 53·8 (SD 8·06) years and two males with a mean age of 65·5 (SD 0·5) years. Of the seven patients one had an associated systemic disease, polyarteritis nodosa, which was diagnosed by satisfying previously published criteria. The treatment regimen for each patient is summarised in Table 2. The scleritis scoring system is detailed in Table 3, and Table 4 summarises the scleritis score for each patient at presentation and at twelve weeks after the commencement of treatment. In five patients there was a significant decrease in the scleritis score at six weeks. This decrese in the scleritis score was maintained over the subsequent observation period. The mean duration of treatment was 7·4 (SD 2·4) months.

Table 5 summarises the present clinical status, complications of treatment, and duration of follow-up. The mean duration of follow-up was 8·4 months, with a minimum of four months. Cyclosporin was

Table 5 *Results of treatment with cyclosporin*

Patient	*Duration of treatment (months)*	*Result*	*Duration of follow-up (months)*	*Complications*
1	4	Remission	4	Tremor
2	5	Relapse, enucleation	7	Tremor, creatinine*
3	8	Remission	13	Creatinine,* hirsutism
4	10	Remission	12	Tremor, hypertension
5	11	Relapse	11	Facial pain
6	6	Remission	8	Tremor, hypertension
7	8	Remission, relapse	4	Tremor, creatinine,* hirsutism, gum hypertrophy

Duration of follow-up was defined as the time from the start of cyclosporin therapy to the present.
*Increase above upper limit of normal.

well tolerated by all but one patient, and only one patient developed side effects that warranted the cessation of therapy. The most common side effects were hirsutism, gum hypertrophy, tremor, hypertension, and mild nephrotoxicity. There were no associated opportunistic infections.

Three patients suffered a relapse in their scleritis on attempted withdrawal of cyclosporin. In patients 2 and 5 disease activity recurred when the cyclosporin dosage was decreased below 5 mg/kg/day, while patient 7 relapsed when the cyclosporin dose was decresed to 3 mg/kg/day. In each case patients were treated with intravenous pulse methylprednisolone therapy and the cyclosporin dosage was increased to 10 mg/kg/day. Patients 5 and 7 responded to this medication with a significant improvement in symptoms and decrease in their scleritis score. Unfortunately patient 2 suffered a perforation of the globe in an area of extensive scleral necrosis and corneal thinning. There was severe disorganisation of the anterior segment and it was decided that enucleation was the most appropriate form of therapy.

There was no difference in clinical features, scleritis score at presentation, or complications between patients who responded to cyclosporin and those who failed to respond to this treatment.

Discussion

Five of the seven patients treated as part of this uncontrolled trial responded to the use of cyclosporin. All had been previously treated with a variety of immunosuppressive agents which had failed to give adequate disease control or were associated with unacceptable side effects. There was no difference between responders and non-responders to treatment with cyclosporin in terms of their previous treatment, associated disease, or scleritis score at presentation.

Cyclosporin has been increasingly recognised as an effective therapeutic agent in the management of a variety of autoimmune diseases.[8] Inflammatory eye disease, particularly uveitis, is often well controlled by the regular use of systemic cyclosporin.[7] The results of the present study indicate that cyclosporin is an effective additional agent in the management of the majority of patients with severe scleritis refractory to other forms of therapy.

Cyclosporin represents the prototype of a new class of drug that appears to work, at least in part, by acting at the level of cytokine production by immune cells.[9] The selective ability of cyclosporin to interefere with the action of interleukin-2 makes it an appropriate agent for the treatment of diseases believed to be mediated by T cells. Although the immunopathogenesis of scleritis is not fully understood, it is believed to be due to immune complex mediated vascular damage to scleral vessels, with the subsequent generation of a granulomatous reaction.[5] T cells have an essential role in the formation of such granulomas, and cyclosporin may act in part by decreasing this component of the inflammatory response.

The widespread use of cyclosporin in the treatment of autoimmune disease has been limited by a concern for the potential side effects, especially its propensity to cause renal, hepatic, and lymphoproliferative disease. This study provides further evidence that such systemic side effects appear to be less prevalent in patients with inflammatory eye disease, in whom severe adverse rections appear to be less frequent, than those seen in patients treated to prevent organ rejection following transplantation.[7] Tremor, hirsutism, hypertension, and raised creatinine levels were all observed complications in our patients. Another problem associated with the use of cyclosporin was the propensity for the scleritis to relapse on attempted withdrawal of the drug. This has been previously observed in the treatment of other autoimmune diseases with cyclosporin and is not always preventable by slowly withdrawing the drug.

The results of the present study indicate that cyclosporin is a potentially useful drug in the treatment of severe scleritis refractory to other immunosuppressive regimens. Unfortunately it is not universally effective, is complicated by frequent, mild side effects, and may be associated with recurrence of disease on attempted drug withdrawal. Despite these limitations we consider that cyclosporin is a useful

additional drug in the management of severe scleritis, and its therapeutic value in the treatment of this disease warrants further investigation.

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