Cyclosporin therapy in Mooren's ulcer

DENIS WAKEFIELD AND *LYON P ROBINSON

*From the School of Pathology, University of New South Wales, Department of Immunology, Prince of Wales Hospital, and the Uveitis and *Corneal Clinics, Sydney Eye Hospital, Sydney, Australia*

SUMMARY Mooren's ulcer is a rare disease of presumed autoimmune aetiology. Some cases run a chronic severe course and fail to respond to local and systemic therapy. We report here such a case with bilateral Mooren's ulcer that failed to respond to local therapy with topical corticosteroids, silver nitrate, and conjunctival resection, as well as systemic immunosuppression with corticosteroids, cyclophosphamide, and azathioprine. Systemic cyclosporin (10 mg/kg/day) resulted in resolution of the corneal ulceration within two weeks of beginning treatment, and the patient has remained in remission after 15 months of therapy. Cyclosporin side effects included hirsutism, hypertension, increased blood levels of urea and creatinine, and abnormalities in liver function tests. All these resolved on reducing the dosage of cyclosporin. The results in this case suggest that cyclosporin is an effective agent in patients with severe sight threatening Mooren's ulcer.

Mooren's ulcer is a chronic ulcerative disease of the cornea of unknown aetiology. Patients with this disease have destruction of the peripheral cornea with marginal ulceration, which progresses circumferentially round the limbus. The ulcer has a characteristic overhanging edge and is associated with stromal destruction. Recent evidence indicates that immune mechanisms may be involved in the pathogenesis of this disease, as affected patients have autoantibodies to conjunctival and corneal epithelium.^{1,2} Furthermore immunoglobulins (IgG and IgE), complement, and mast cells have been found in the conjunctival epithelium adjacent to ulcers.³ Other patients have been shown to have abnormalities in cell mediated immunity, including the demonstration of positive migration inhibition factor tests in response to corneal antigens,⁴ and abnormalities in peripheral blood T cell subsets.⁵ These observations have led to the hypothesis that the abnormalities in this disease may be the result of T cell mediated mechanisms or abnormalities in T cell control. Therefore it seemed logical to suspect that the relatively T cell selective immunosuppressive agent cyclosporin may be effective in the treatment of this disease.

We describe here the successful use of systemic cyclosporin in a patient with severe, previously refractory, bilateral Mooren's ulcer.

Case history

A 31-year-old Caucasian female presented in the third month of her third pregnancy in December 1982 with bilateral corneal ulceration. Initial treatment consisted of topical corticosteroids. However, her disease remained clinically active until she was referred to one of us (LPR) in March 1984.

Visual acuity was 6/9 in the right eye and 6/60 in the left eye. The right cornea had two large ulcerated areas with undermined edges extending from 6.30 to 8.30 o'clock, about 2 mm from the limbus. The left cornea was severely damaged and had a healed ulcer running through 360° with some active ulceration in the limbal area at 7.30 (Fig. 1). The whole cornea was very thin. There was no significant associated systemic disease. Four weeks after her initial consultation there was perforation of the ulcer in the active ulcerating area of the left eye.

The patient underwent a successful penetrating keratoplasty of the left eye (disparate donor graft size 9.5 mm in 9.0 mm). Four weeks after the operation the graft suddenly became oedematous and there were changes indicative of graft rejection. The patient was treated with topical prednisolone acetate eye drops and subconjunctival betamethasone. At the same time the right eye developed several small superficial infiltrates in the peripheral cornea at 6.30 and 11.00 o'clock. The patient was started on naproxen (250 mg bd) and colchicine (0.5 mg tds),

Correspondence to Professor D Wakefield, University of New South Wales, PO Box 1, Kensington, New South Wales, Australia.

Fig. 1 Typical area of active Mooren's ulceration involving the temporal cornea of the left eye. Note the undermined central ulcer edge and corneal infiltrate in the leading edge. There are prominent areas of new vessel ingrowth in the ulcer floor. The adjacent peripheral conjunctiva is injected and elevated.

with little effect on the signs of corneal graft rejection. Subsequently she was given pulsed doses of intravenous methylprednisolone (MP)—1 g intravenously on three occasions during the first week and subsequently 500 mg intravenously at weekly intervals for the next four weeks. The area of corneal ulceration appeared to heal on this pulsed steroid regimen. There was some clearing of the corneal oedema in the left corneal graft.

The patient was subsequently started on oral prednisolone, beginning with 50 mg in the morning and cyclophosphamide 100 mg in the morning (2 mg/kg/day). On this regimen the corneal ulcers in the right eye recurred and required debridement and resection of the adjacent conjunctival area. At the same time the area of active inflammation was treated topically with 1% silver nitrate. The right cornea subsequently healed and the left corneal graft remained clear. The prednisolone therapy was subsequently reduced at a rate of 2.5 mg weekly. The corneal graft in the left eye remained clear, though there was recurrence of ulceration in the right eye.

Three months after the start of cyclophosphamide the disease flared up in the right eye with an area of confluent corneal staining running along the inferior margin from 5.00 to 8.00 o'clock. There were several small oval areas of staining in the normal cornea at 10.00, 3.00, and 4.00 o'clock. The left graft became oedematous, and keratic precipitates were present on the lower third of the cornea. The patient was given an increasing dosage of prednisolone of 100 mg

in the morning and started on azathioprine 100 mg (2 mg/kg/day) in the morning. Over the next two weeks there was improvement in the right eye and clearing of the left corneal graft. The patient was nauseated by the medication and developed abnormal liver function as well as marked cushingoid side effects from the steroids. The previously normal results of the liver function tests showed a marked elevation in the alkaline phosphatase (186 U/l; normal range 25–110 U/l), gamma glutaryl transferase (GGT) (239 U/l; normal range 5–50 U/l), aspartate transaminase (76 U/l; normal range 5–35 U/l), and alanine transaminase (65 U/l; normal range 5–35 U/l). At the same time there was recurrence of ulceration in the right eye, and a decision was made at this stage to give the patient cyclosporin 20 ml (10 mg/kg/day) daily.

Two weeks after the start of this therapy there was marked improvement in the right eye, with only mild staining along the ridge separating the normal cornea from the previously ulcerated area. The left cornea cleared. Visual acuity in the right eye was 6/6 and in the left eye was 6/9. Four weeks after the start of the cyclosporin the prednisolone dosage was decreased to 37.5 mg and the cyclosporin dosage decreased to 15 ml daily. The right eye continued to remain clear, with no signs of active ulceration, and the left corneal graft remained clear, with visual acuity of 6/9.

Over the next six months the prednisolone therapy was decreased gradually, and finally withdrawn with no relapse of the disease. Cyclosporin was subsequently decreased, at a rate of 2.5 ml/month. The patient is at present on no systemic medication, with no evidence of disease relapse after 15 months of therapy.

Side effects due to cyclosporin included marked facial and body hirsutism, increased blood pressure (150/100 mmHg), which was controlled with propranolol 20 mg bd, a raised blood urea (10.5 mmol/l) and creatinine (0.13 mmol/l; normal range 0.06–0.11 mmol/l) and abnormal liver function tests as outlined above. The patient tolerated these symptoms well and all side effects have subsequently abated on the reduced dosage of cyclosporin.

RESULTS OF INVESTIGATIONS

On presentation the patient's erythrocyte sedimentation rate was 15 mm/h. The white cell count was $11.2 \times 10^9/l$ with 85% neutrophils and 7% lymphocytes. The haemoglobin was 13.6 g/dl. The urea was 4.8 mmol/l and the creatinine was 0.08 mmol/l. Tests for antinuclear antibody and rheumatoid factor were negative. Serum immunoglobulins were within the normal range with an IgA of 1.3 g/l (normal range 0.7–4.5 g/l), IgG of 8.5 g/l (normal range 7–16 g/l), IgM of 2.4 g/l (normal range 0.8–2.5 g/l), and an IgE of 3 IU/l (normal range 0–150 IU/l). The total

haemolytic complement (CH50) was 87% (normal range 68–138%), the Clq was 0.15 g/l (normal range 0.15–0.23 g/l), the C4 was 0.43 g/l (normal range 0.17–0.46 g/l), and the C3 was 0.92 g/l (normal range 0.65–1.26 g/l), all within the normal range. The patient was anergic on delayed hypersensitivity skin testing with tuberculin, and mumps, candida, tetanus, streptococcal, and trypanophyton antigens. Analysis of the T cell subsets revealed $0.4 \times 10^9/l$ helper (OKT4) T lymphocytes (normal range 0.7 – $0.17 \times 10^9/l$), $0.2 \times 10^9/l$ suppressor (OKT8) T lymphocytes (normal range 0.4 – $1.0 \times 10^9/l$), $0.6 \times 10^9/l$ T (OKT 11) lymphocytes (normal range 1.0 – $2.3 \times 10^9/l$), and the Ia positive cells were $0.14 \times 10^9/l$ cells (normal range 0.05 – $0.25 \times 10^9/l$). The T4:T8 ratio was 2.3 (normal range 1.2–2.7).

Discussion

Cyclosporin has been shown to be effective in suppressing the underlying autoimmune response in a variety of inflammatory diseases of the eye, especially uveitis, and recently in two complicated cases with a peripheral corneal melting syndrome complicating Wegener's syndrome and scleritis.^{6,7} In our patient cyclosporin was introduced after an adequate trial of a variety of other immunosuppressive agents, including systemic corticosteroids, azathioprine, and cyclophosphamide. Each of these immunosuppressive agents has been previously reported to be of value in the management of patients with Mooren's ulcer.⁸ However, none of these medications alone or in combination controlled the ocular disease process in this case. Following the introduction of cyclosporin there was resolution of the Mooren's ulcer, and the disease was well controlled for the duration of follow-up.

The mode of action of cyclosporin is not completely understood, but appears in part to be related to the generation of interleukin 2 by helper T cells.⁹ The selective ability of cyclosporin to interfere with the action of IL2 makes it an ideal agent for the treatment of diseases that are believed to be mediated by T cells. Rahi² has recently reported T cell abnormalities in a patient with Mooren's ulcer, and the results in our case confirm such T cell abnormalities (T cell lymphopenia and anergy) in patients with Mooren's ulcer.

Cyclosporin has a number of well characterised side effects, some of which were observed in our patient.¹⁰ These include the marked hirsuting effect of this drug when used over a long period of time. The patient also had a consistently raised blood urea and

creatinine, together with abnormal liver function tests. Elevated blood pressure has also been previously reported as a complication of cyclosporin treatment.¹¹ Nussenblatt *et al.*¹¹ have recently reviewed the systemic side effects of cyclosporin in patients with uveitis, and these appear to be less severe than in patients receiving cyclosporin for transplantation and graft rejection related disorders. A number of reasons have been proposed for this observation, including the fact that lower doses of cyclosporin are required to control these diseases than are required in patients undergoing organ transplantation. The most worrying side effect of cyclosporin, namely lymphomas, appears also to be less frequent in patients treated with this drug for diseases not associated with organ transplantation.¹²

This case report illustrates the therapeutic benefit of cyclosporin in a previously refractory case of Mooren's ulcer. Our observation highlights the possible involvement of T cell mediated mechanisms in the pathogenesis of this disease and suggests that a controlled trial should be undertaken of the use of cyclosporin in severe refractory cases of Mooren's ulcer.

References

- 1 Shaap OL, Feltkamp TEW, Breebaart AC. Circulating antibodies to corneal tissue in a patient suffering from Mooren's ulcer (ulcus rodens corneae). *Clin Exp Immunol* 1969; **5**: 365–70.
- 2 Brown SI, Mondino BJ, Rabin BS. Autoimmune phenomena in Mooren's ulcer. *Am J Ophthalmol* 1976; **82**: 835–40.
- 3 Mondino BJ, Brown SI, Rabin BS. Cellular immunity in Mooren's ulcer. *Am J Ophthalmol* 1978; **85**: 788–91.
- 4 Mondino BJ, Brown SI, Rabin BS. Autoimmune phenomena of the external eye. *Ophthalmology* 1978; **85**: 801–17.
- 5 Rahi AHS. Pathology of Mooren's ulcer. *Br J Ophthalmol* 1984; **68**: 182–7.
- 6 Nussenblatt RB, Palenstine AG, Chan CC. Cyclosporin A therapy in the treatment of intraocular inflammatory disease resistant to corticosteroids and cytotoxic agents. *Am J Ophthalmol* 1983; **96**: 275–9.
- 7 Kruit PJ, Van Balen A Th M, Stilma JS. Cyclosporin A treatment in two cases of corneal peripheral melting syndrome. *Doc Ophthalmol* 1985; **59**: 33–9.
- 8 Foster CS. Immunosuppressive therapy for external ocular inflammatory disease. *Ophthalmology (Rochester)* 1980; **87**: 140–9.
- 9 Shevach EM. The effects of cyclosporin A on the immune system. *Ann Rev Immunol* 1985; **3**: 397–423.
- 10 Strom TB. Cyclosporin induced nephrotoxicity. *N Engl J Med* 1984; **311**: 728–30.
- 11 Nussenblatt RB, Rouk AH, Wacker WBR, Palenstine A, Scher I, Gery I. Treatment of ocular inflammatory disease with cyclosporin A. *Lancet* 1979; **ii**: 235–8.
- 12 Anonymous. Cyclosporin and neoplasia (Editorial). *Lancet* 1983; **i**: 1083.

Accepted for publication 31 July 1986.