Short term cyclosporin A treatment of Behçet's disease

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SUMMARY Eleven separate three-month courses of cyclosporin A, an oral solution 10 mg/kg/day, were administered to eight patients with Behçet's disease with sight-threatening posterior uveitis. It was found to be effective in arresting the inflammatory activity in the eye as well as the mucocutaneous lesions of Behçet's disease. Improvement in visual acuity was observed within one week of starting therapy. Severe exacerbations in the ocular and mucocutaneous lesions occurred on withdrawal of the drug. At this dosage side effects included hirsutism in all women, and a slight rise of serum bilirubins in two patients and of blood urea in one patient. The latter two conditions responded rapidly to dose adjustment.

The triple symptom complex comprising recurrent oral and genital ulcerations and relapsing iritis was first described by Behçet in 1937.¹ In addition to the eye lesions conjunctivitis, episcleritis, keratitis, haemorrhage, and cellular infiltration of the vitreous body, originally described retinitis, retinal thrombophlebitis, optic atrophy, and papilloedema have been reported.^{2,3} It later became apparent that Behçet's disease is a systemic disorder involving many other organs including joints, blood vessels, the central nervous system, and the gastrointestinal system.⁴ The ocular involvement seen in about 47% of cases may lead to complete loss of vision in 15% of them.⁵ Studies in rats suggest a pathogenetic role of the retinal S antigen in the development or perpetuation of posterior uveitis.⁶ In man triggering this phenomenon in Behçet's disease is unknown.

Cyclosporin A, a potent immunomodulator affecting both the cellular and humoral arms of the immune response,⁷ has been found to be effective in the control of inflammatory activity in the eyes of patients with posterior uveitis of non-infectious origin.^{8,9} In this investigation 11 separate three-month courses of cyclosporin A oral solution were administered to eight patients with Behçet's disease

with sight-threatening uveitis, and its effects on the various manifestations of the disease were assessed. Seven of the patients were followed up for six to 24 months.

Patients and methods

Eight patients with sight-threatening posterior uveitis were included in this study. Behçet's disease was diagnosed in all patients according to the criteria proposed by O'Duffy,¹⁰ requiring three of the following five features to be present either previously or at first attendance: aphthous stomatitis, genital ulcers, dermal vasculitis, uveitis, or arthritis. Either aphthous stomatitis or genital ulcers had to be present for a definite diagnosis. In addition tissue typing and the pathergy test, a non-specific skin hypersensitivity reaction to needle prick, were carried out on each patient. The combined use of HLA B5 and pathergy positivity has previously been reported from this laboratory to be a useful diagnostic marker of Behçet's disease in Turkey.¹¹ All the eight cases had acute sight-threatening posterior uveitis and retinal vasculitis. Six patients received a three-month course of cyclosporin A. One patient received two and another patient received three separate three-month courses. All patients were required to attend the clinic regularly once a week

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during the first month and biweekly thereafter, and to report new complaints immediately. Follow-up periods ranged from six to 24 months from the beginning of therapy.

Cyclosporin A solution 10 mg/kg/day was given by mouth in one dose in the morning. If it caused serious side effects the dose was reduced to 8-6 mg/kg/day. All other anti-inflammatory and immunosuppressive medications were discontinued as rapidly as possible.

Disease activity in each of the 16 eyes was assessed under four headings: (a) anterior chamber, (b) vitreous cavity, (c) fundi, (d) visual acuity. The last was recorded according to the Snellen chart.

Standard methods were used for the enumeration of peripheral blood lymphocytes, E rosette forming cells (T cells), surface Ig-bearing cells (B cells), and the response of blood lymphocytes to phytohaemagglutinin in cultures.¹² In-vivo skin reactivity was assessed by the purified protein derivative (PPD) skin test.

Results

OCULAR DISEASE (Tables 1 and 2)

The anterior chamber was involved in eight and normal in eight eyes before therapy. At the end of three months' therapy with cyclosporin A nine eyes remained unchanged, the inflammatory activity regressed in four eyes and progressed in three eyes.

Vitreous opacities were present in 13 eyes, one was

normal, and two could not be examined. At the end of therapy cellular infiltrations had regressed in six, increased in two, and were unchanged in six eyes.

Before treatment optic atrophy was present in two eyes, papilloedema in two, macular oedema in four, periphlebitis with haemorrhages and exudates in four, and subhyaloid haemorrhage in one. One eye was normal, and two eyes could not be visualised because of opacified media. At the end of three months' therapy macular oedema had disappeared in three of four eyes and cicatrix formation was observed in the fourth eye. Papilloedema regressed in the two eyes. Vasculitis in the form of periphlebitis, haemorrhages, and exudates regressed in two eyes and remained unchanged in the remaining two. Subhyaloid haemorrhage observed in one eye had regressed by the end of treatment. One normal fundus remained normal. Two fundi were still impossible to visualise.

Visual acuity, reflecting the effects of therapy in all the segments involved, improved in 12 eyes, was unchanged in three, and was worse in one (Table 3).

A rebound phenomenon was observed in all but one case on the withdrawal of cyclosporin A. Cellular infiltrations increased in eight cases previously involved, and anterior uveitis started in four previously uninvolved eyes. Vitreous opacities were observed in all the 13 eyes previously involved and started de novo in one eye. The retinal lesions became more severe in 12 eyes, two eyes were unchanged, and two fundi could not be visualised. One patient (case 5), who did not show any signs of inflammatory reactivation in the eye, had been on long term immunosuppression with cyclophosphamide and steroids before cyclosporin (Table 2).

The follow-up of patients from the end of therapy showed the following findings. The first two patients who had received three and two three-month courses of cyclosporin A treatment respectively ran a stormy course, having frequent attacks of posterior and anterior uveitis. Although they were subsequently put on immunosuppressive therapy with cyclophosphamide, the first developed bilateral optic atrophy and the second unilateral optic atrophy in 24

Table 1 Clinical data

No.	Age, sex	Oral	Genital	EN	Ocular	Arthritis	Vascular
1	33, M	+	+	-	+	+	+
2	22, M	+	-	+	+	-	+
3	24, F	+	+	+	+	-	-
4	32, F	+	+	-	+	+	-
5	29, M	+	-	-	+	+	-
6	34, M	+	+	+	+	-	-
7	23, F	+	+	-	+	-	-
8	33, M	+	+	+	+	+	±

EN=erythema nodosum.

Table 2 Disease activity before, during, and after cyclosporin A

	Before	During	After*
Mucocutaneous	8/8	2/8	8/8
Erythema nodosum	3/8	0/8	5/8
Ocular (16 eyes)	16/16	4/16	15/16
Joints: arthralgia	3/8	3/8	3/8
arthritis	0/8	0/8	1/8
Vascular: acute	0/8	0/8	0/8
chronic	3/8	3/8	3/8
Central nervous system	0/8	0/8	0/8

*Two weeks after the withdrawal of cyclosporin A.

Table 3 Summary of the effect of cyclosporin A on activity of ocular disease

	Number of eyes that could be examined	Better	Unchanged	Worse
Anterior chamber	16	4	9	3
Vitreous	14	6	6	2
Retina	14	8	5	1
Visual acuity	16	12	3	1

months after the beginning of cyclosporin A treatment. The third and fourth patients, both female, became stabilised after the acute exacerbation period on termination of therapy. Although they still had minor attacks of posterior uveitis, they did not develop irreversible changes in the fundi and maintained fair visual acuity in both eyes. The fifth patient had the most stable course among the eight cases; he had been on chronic immunosuppressive therapy with cyclophosphamide and prednisolone before cyclosporin A and was maintained on a lower dose of both drugs after the initial therapy. He experienced no rebound phenomenon on cessation of cyclosporin A, and his vision remained unchanged for 18 months. The sixth patient was lost to follow-up. The seventh and eighth cases were still running fulminant courses 6-9 months after the cessation of cyclosporin A therapy.

EXTRAOCULAR DISEASE

Mucocutaneous involvement comprising aphthous stomatitis, genital ulcers, and folliculitis was improved by cyclosporin A in seven of eight cases. In six cases manifestations of cutaneous disease disappeared completely during treatment. In one patient the frequency, duration, and severity of the oral aphthae diminished during therapy. A rebound phenomenon was observed within one week after the end of therapy in all patients and lasted for several weeks. Erythema-nodosum-like lesions, which were present in three cases before therapy subsided completely during the three months of therapy. Five cases, two of which did not have these lesions before cyclosporin, developed them within two weeks after the end of therapy (Table 2).

Arthralgias reported in three cases before therapy were not influenced by cyclosporin A. One patient who did not have joint complaints before developed arthritis of the left malleolar joint within three weeks after the end of therapy. Four patients with deep vein thrombosis or sequelae of thrombophlebitis did not show any changes during or after therapy.

IMMUNOLOGICAL EFFECTS

Skin reactivity assessed by the PPD skin test was positive in five and negative in three cases before therapy. It remained positive in four of the five cases during therapy. One case was not retested. The mean lymphocyte count in eight cases before therapy was 1.86 (SD 0.67) $\times 10^9/l$ and did not differ significantly from the post-treatment value of 1.47 (SD 0.82) $\times 10^9/l$. The mean percentage and absolute number of E rosetting cells (T cells) 42% and 0.78 (SD 0.23) $\times 10^9/l$ respectively were similar to the post-therapy counts, 49.5% and 0.73 (SD 0.30) $\times 10^9/l$, respectively. The mean percentage of phytohaemag-

glutinin responding cells in short term lymphocyte cultures was 54% before treatment and 66% after treatment. The difference was not significant. OKT4/OKT8 ratios determined in two cases did not show appreciable changes from pretreatment values or from normal controls.

SIDE EFFECTS

Measurements of body weight, pulse rate, blood pressure, complete blood counts, determination of serum urea, creatinine, liver function tests, and urine analyses were performed once a week during the first month and once a month thereafter. Paraesthesias, hyperaesthesias, and flatulence/nausea were the most common complaints from the first days of therapy. They were not serious enough to cause modification of the drug dosage. Hypertrichosis developed in each of the three female patients. It started during the second month of therapy and lasted several months after withdrawal, causing serious anxiety but not early cessation of therapy. Mild hyperbilirubinaemia observed in two cases responded promptly to the reduction of the dose of cyclosporin A to 8 mg/kg/day. One patient developed hypertension and urea retention, both of which returned to normal values on dose reduction to 6 mg/kg/day. The same patient developed progressive anaemia not accompanied by other haematological changes. On questioning, one patient complained of a decrease in libido, probably caused by hyperaesthesia in the penis during intercourse (Table 4).

Discussion

Cyclosporin A, in a dose of 10 mg/kg/day, was found to be effective in arresting the inflammatory activity in the eye of patients with Behçet's disease, resulting in a definite improvement in visual acuity. The improvement was rapid. Cellular infiltrates in the vitreous receded within one to two weeks, retinal vasculitis regressed more slowly, and improvement in visual acuity preceded the regression of inflammatory activity by several days in most of the patients. Acute exacerbations of anterior uveitis were also favour-

Table 4 Frequency of side effects of short term cyclosporin A

Paraesthesia/hyperaesthesia	6/8
Flatulence/nausea	7/8
Hirsutism	3/8 (all females)
Hyperbilirubinaemia	2/8
Hypertension	1/8
Urea retention	1/8
Anaemia	1/8
Decrease in libido	1/8

ably affected in a few cases. During the three-month therapy period the mucocutaneous disease showed very little activity, indicating an anti-inflammatory action on the non-ocular manifestations as well.

All the patients except one experienced acute exacerbations in the ocular and mucocutaneous diseases within one week after the withdrawal of cyclosporin A at the end of three months. It was noted that, although cyclosporin seemed to be less effective in controlling the inflammatory activity in the anterior chamber, on its withdrawal a flare-up of inflammatory activity occurred in the anterior chamber as well as the posterior segment of the eye. The acute increase in the inflammatory activity in all the segments resulted in a significant decrease in visual acuity. The rebound phenomena observed in the mucocutaneous disease accompanying acute exacerbations in the ocular manifestations suggest the possibility of a generalised increase in the inflammatory activity in all the organs usually involved in Behçet's disease.

In order to ascertain the long term effects of cyclosporin A on the outcome of ocular involvement in Behçet's disease, all the cases but one are being followed up closely. The first two patients who have been followed up the longest have continued to have frequent ocular attacks resulting in serious damage. In the last two patients the disease seemed to behave similarly during the first six to nine months off therapy. Three patients who did not have as severe rebound phenomena as the others seem to run more stable courses off therapy. Since all these patients had been selected for cyclosporin A therapy because of their fulminant, sight-threatening ocular disease, this result does not seem as discouraging as it appears.

The mode of action of cyclosporin A on the various inflammatory phenomena in Behçet's disease is unknown. Various immunological disturbances have been reported in Behçet's disease,^{13,14} but there is no direct evidence that the inflammatory lesions in various organs are immunologically mediated. Cyclosporin A is thought to influence the early phase of the immune response by blocking the synthesis and/or release of IL-1 from macrophages and IL-2 from helper T cells.^{15,16} If this blockade is the cause of the anti-inflammatory action of cyclosporin A, it is rapid and transitory. To gain any lasting benefit a long term treatment plan with cyclosporin A with

or without other immunosuppressive or anti-inflammatory drugs should be considered.

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