

Low dose cyclosporin A versus pulsed cyclophosphamide in Behçet's syndrome: a single masked trial

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Abstract

A single masked trial of cyclosporin A 5 mg/kg/day versus monthly 1 g intravenous boluses of cyclophosphamide was conducted among 23 patients with Behçet's syndrome and active, potentially reversible uveitis. The trial was unmasked after a mean of 12 (SD 2) months for the cyclosporin A group ($n=12$) and a mean of 10 (SD 3) months for the cyclophosphamide group ($n=11$). During the initial 6 months the visual acuity significantly improved ($p<0.001$) in the cyclosporin A group whereas this was not observed in the cyclophosphamide group. The subsequent follow-up of patients up to 24 months suggested that the initial improvement in visual acuity with cyclosporin A was not sustained. More extensive and especially long-term studies of cyclosporin A in the uveitis of Behçet's syndrome are warranted.

Eye involvement occurs in approximately half of the patients with Behçet's syndrome and may also lead to blindness in around one fifth.¹ Recently many open trials²⁻¹² and one masked trial¹³ of cyclosporin A reported favourable results in treating eye disease in Behçet's syndrome. However the dose of cyclosporin A used in these studies was high (6-10 mg/kg/day) according to the recent understanding of the toxicity of this drug.^{14,15} Furthermore in some of these studies patients with non-Behçet's uveitis (that is, endogenous uveitis, Vogt-Koyanaga Harada syndrome) were included.^{3,7,11,12} This makes the interpretation of the results of these trials difficult. Here we report a pilot, controlled, and single masked trial of low dose (5 mg/kg/day) cyclosporin A versus cyclophosphamide (1000 mg intravenous bolus/month) in 23 Behçet's patients with severe eye involvement. The trial was unmasked 7 months after the entry of the last patient due to the observed and reported¹⁶ efficacy of cyclosporin A in treating Behçet's syndrome. The subsequent follow-up of the trial patients using cyclosporin A up to 24 months is also reported.

Patients and methods

Twenty three Behçet's patients with active potentially reversible eye disease were studied at Behçet's Syndrome Outpatient Clinic at Cerrahpaşa Medical Faculty. The make-up of this clinic is described in detail elsewhere.¹ All patients had bilateral severe uveitis with mainly posterior involvement and at least three ocular disease exacerbations (attacks) within the pre-

ceding 6 months. Patients who had end stage disease, with mainly irreversible retinal damage and blindness preventing their evaluation, were excluded. All patients fulfilled the recently reported international diagnostic criteria.¹⁷

At the beginning of the trial the patients were assigned alternatively to receive either cyclosporin A solution 5 mg/kg/day or monthly intravenous boluses of 1000 mg of cyclophosphamide after an explanation of the investigative nature of the study and obtaining their consent. However they were free to choose either treatment modality irrespective of their initial allocation. The mean weight of the patients to receive cyclosporin A was 66.4 (SD 10.4) kg and the mean weight of those to receive cyclophosphamide was 64.0 (SD 9.7) kg.

Cyclosporin A solution was given by mouth in two divided doses. All patients were required to attend the clinic once a week during the first month and monthly thereafter. Measurements of body weight, pulse rate, blood pressure, serum creatinine, and serum cyclosporin A levels were performed at each visit and total blood counts, liver function tests (ALT, AST, bilirubin, and alkaline phosphatase), and urinalyses every 3 months. Each month 1000 mg doses of cyclophosphamide were given intravenously in 1 litre of 5% dextrose solution over 1 hour. Total blood and platelet counts were done on each visit before pulsed cyclophosphamide therapy.

A full ophthalmological evaluation was performed by the same observer (YÖ) who was initially masked to the outcome of drug allocation. Special attention was given to visual acuity and the occurrence of eye attacks. The visual acuity in evaluating the results was expressed by taking the mean of the numerators for each eye on a 0-10 Snellen chart. A new attack was defined as an increase or development of inflammatory cells in anterior chamber, flare, vitreous haze, all graded on a 0-4+ scale. Furthermore, the mere presence or absence of retinal vasculitis, macular oedema, vascular sheathing, venous occlusion, and vitreous condensation were also recorded at each visit. Of these parameters the emergence of macular oedema or of retinal vasculitis was also interpreted as an indicator of a new attack. Dermatological evaluation was graded as 'worse' (-1), 'same' (0), 'better' (+1), both by the patient and the dermatologist (again single masked). An internist (SY) ran the study as the primary care physician and made the necessary dose adjustments. No patient had been taking immunosuppressive drugs during the preceding 6 months of entry to the trial. However there were three patients taking steroids.

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One patient was in the cyclosporin A group taking prednisolone 20 mg every other day and two were in the cyclophosphamide group, one using 10 mg and the other 5 mg/day of prednisolone.

The study was initially planned to last 24 months. Seventeen months from the entry of the first and 7 months after the last patient the trial was unmasked due to the apparent beneficial effects of cyclosporin A observed by the non-masked members of the study group and similar reports of investigators from other centres.¹⁶ However during the open phase the formal monthly evaluations of the patients were carried out up to 24 months.

Results

Table 1 shows the demographic characteristics, the disease duration, and severity of eye disease at the time of entry into the trial. All patients had bilateral eye disease. It was noted that all 12 patients using cyclosporin A were males as the females refused to use cyclosporin A because of risk of potential hirsutism. There were however six males and five females in the cyclophosphamide group. The mean age at entry, duration of eye disease, and the mean visual acuity were similar between the two groups. There were no statistically significant differences in the scores of inflammatory cells and flare in the anterior chamber and vitreous haze between the two groups at the onset of the trial.

The trial was unmasked after a mean of 12.30 (SD 2.36) months for the patients in the cyclosporin A group and 9.80 (SD 3.42) months for those in the cyclophosphamide group ($t=1.90$, $0.10 > p > 0.05$). During this time two patients from the cyclosporin A group were lost from the trial. One was at month 9 when he developed hepatitis B and had to be withdrawn. The second

one was a no-show after 3 months. During the same time there was one loss at month 11 from the cyclophosphamide group for unknown reasons. After the trial was unmasked there were two further losses from the cyclosporin A group at months 11 and 21, again without apparent causes.

Only four patients from the cyclophosphamide group completed the 24 months continuing to use bolus cyclophosphamide. Of the remaining six patients four were switched to cyclosporin A, one to oral cyclophosphamide, and one to weekly doses of methotrexate.

The mean dose of cyclosporin A which could be used was 4.89 (SD 0.54) mg/kg/day during the first 6 months of the masked period and 4.49 (SD 0.94) mg/kg/day during the rest of the trial ($t=1.60$, $p > 0.10$). The mean plasma level of cyclosporin A was 131.20 (SD 13.80) ng/ml during the masked phase. Plasma levels were not routinely done during the open phase. Among the eight patients who completed the full 24 months using cyclosporin the mean serum creatinine level at the time of entry was 70 (SD 7.01) $\mu\text{mol/litre}$ and 79 (SD 17) $\mu\text{mol/litre}$ at their last visit ($t=2.02$, $0.10 > p > 0.05$). No patient had to be withdrawn due to any form of drug toxicity.

The alternate day steroid that was being used in one patient in the cyclosporin A group was gradually tapered down and was stopped at 9 months. This was the same patient that had to be withdrawn because of hepatitis B. The steroid use in two patients in the cyclophosphamide group was stopped after the first month.

Table 2 depicts the mean visual acuity at four different points in the trial and shows that visual acuity significantly improved when compared with that observed at entry in the cyclosporin A group at 6 months ($p < 0.001$). This initial improvement however had disappeared by the time the trial was unmasked. The visual acuity among the eight patients continuing to use cyclosporin A at the end of 24 months remained approximately the same as that at the time of unmasking the trial or as that at entry. No statistically significant change in visual acuity occurred at the three time points, apart from a trend to deterioration at the time of unmasking the trial when compared with that at the time of entry.

As seen in Table 3 although there was a trend for fewer ocular attacks in the cyclosporin A group this did not assume statistical significance for the time intervals assessed.

Statistical analysis of other pathology related to the eye (retinal vasculitis, macular oedema, etc.) was not attempted because of few events in a small number of patients. Although the effect of cyclosporin A and cyclophosphamide on the extraocular manifestations of the disease were also recorded again there were too few events in our small group of patients to perform a formal analysis.

Discussion

During the initial 6 months the most relevant outcome of eye involvement, the visual acuity, fared significantly better among the cyclosporin

Table 1 Patient characteristics

	Number	Male/ female	Age at entry (years)	Duration of eye disease (years)	Mean visual acuity at entry
Cyclosporin A	12	12/0	29 (6)* (15–39)†	2.64 (1.58) (1–5.5)	4.46 (2.96)
Cyclophosphamide	11	6/5	32 (6) (25–41)	2.39 (2.37) (0.5–8)	4.77 (2.65)

*SD in parenthesis.

†Range.

Table 2 Visual acuity

	At entry	At 6 months	At the time of unmasking of the trial*	At 24 months
Cyclosporin A	4.46 (2.96)† (n=12)	6.82 (2.98)‡ (n=11)	4.75 (4.84) (n=10)	4.50 (2.94) (n=8)
Cyclophosphamide	4.77 (2.65) (n=11)	4.14 (3.09) (n=11)	3.95 (2.30) (n=10)	not comparable

*See text for duration of the masked periods for each group.

†SD in parenthesis.

‡ $t=5.47$, $p < 0.001$ versus visual acuity at entry (paired t test).

Table 3 Number of ocular attacks per patient per month

	Up to 6 months	From 6 months to the time of unmasking of the trial	From the time of unmasking of the trial to 24 months
Cyclosporin A	0.48 (0.28)*† (n=11)	0.49 (0.52) (n=10)	0.51 (0.46) (n=8)
Cyclophosphamide	0.62 (0.22)† (n=11)	0.60 (0.51) (n=10)	not comparable

*SD in parenthesis.

† $t=1.30$, $p > 0.02$.

A users compared with those using cyclophosphamide. Even though only a small number of patients could be studied it was possible to demonstrate this effect. The 6 month interval was arbitrarily chosen as a convenient time span when the effect of the two medications could be compared between the maximum number of patients from each group. Furthermore in the allocation of patients to the treatment groups there was a definite bias towards females among the cyclophosphamide users. This was mainly due to patient refusal of cyclosporin A because of risk of potential hirsutism.¹⁴ Behçet's syndrome runs a more severe course in the male and this is also true for eye disease.¹ Thus the more beneficial effect of cyclosporin A compared with cyclophosphamide would perhaps have been more apparent had there been a more even sex distribution of the patients.

The long term effect of cyclosporin A on visual acuity as observed in this study was somewhat disheartening especially in the light of the favourable effect noted during the early phase. It can be said that the visual acuity during the open phase cannot legitimately be compared with that in the masked phase because of possible observer bias. However as noted in Table 2 the trend for dampening of the beneficial effect of cyclosporin A begins before the time when the code is revealed. On the other hand the preservation of the mean visual acuity among the eight patients who completed the full 24 months can be taken as a clue to the efficacy of cyclosporin A in the treatment of eye disease in Behçet's syndrome. In a placebo controlled study of azathioprine recently reported by our group¹⁸ the mean visual acuity had significantly deteriorated among the placebo users after 24 months. It is to be noted that in the azathioprine study¹⁸ the patients had not been specifically selected for active eye disease as was the case in the current study.

We believe that cyclosporin A is a useful and, currently, perhaps the most effective agent for the treatment of eye disease in Behçet's syndrome. This seems especially true for its short term use. Its potential usefulness over longer

periods however needs to be further elucidated by carefully conducted studies in greater number of patients using acceptable doses.

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