

Cyclosporin A in the treatment of chronic demyelinating polyradiculoneuropathy

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Abstract

Eight patients with chronic inflammatory demyelinating polyneuropathy, five of whom had an associated paraproteinaemia, were treated with cyclosporin in a pilot, uncontrolled study for periods up to three and a half years after failing to respond adequately to corticosteroid and azathioprine therapy and plasmapheresis. Three patients had an excellent response, two with complete remission. In other cases it was possible to reduce the corticosteroid therapy and frequency of plasmapheresis. There were no serious complications of the treatment.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disease of the peripheral nerves with a relapsing and remitting, or progressive course.¹⁻³ It is thought to be an autoimmune disorder, but it is unclear to what extent humoral and cellular immune factors are involved in the mediation of nerve damage. However, T cells and macrophages infiltrate the nerve and there is increased expression of class II major histocompatibility complex (MHC) molecules in nerve tissue that suggests gamma interferon or other lymphoid cytokines are released by these infiltrating cells.⁴ Some cases of chronic demyelinating neuropathy, with identical clinical and pathological features to CIDP have an associated benign monoclonal gammopathy (chronic paraproteinaemic demyelinating neuropathy).

Both prednisone and plasmapheresis have improved the clinical course of many patients with chronic demyelinating polyneuropathy, with and without paraproteinemia.⁵⁻⁷ There are some patients who fail to respond to these forms of therapy. Cytotoxic agents such as azathioprine⁸ and cyclophosphamide have been used, but with limited success and some toxicity. Total lymphoid irradiation has also been tried with only partial success.⁹ Thus there remains a need for alternative therapy for some patients with this condition. Cyclosporin A (C_sA), a fungal metabolite, has a widespread clinical use both in transplantation and in autoimmune diseases.¹⁰⁻¹³ In this study we report the results of an uncontrolled pilot study of C_sA in the treatment of chronic demyelinating polyneuropathy in eight patients, five of whom had an associated paraprotein, who had failed to respond to treatment with corticosteroids, immunosuppression and plasmapheresis.

Methods

Patient selection

All patients had received a clinical and laboratory evaluation for peripheral neuropathy, including electrophysiological studies and sural nerve biopsy. The diagnosis of CIDP was made according to accepted criteria¹⁻³; we included in the study five patients who also had a benign paraproteinaemia. All eight patients had received adequate treatment with prednisone and plasmapheresis, and five also had been given azathioprine and one cyclophosphamide. Before starting C_sA, each patient had a full neurological examination and the following laboratory investigations: full blood count, erythrocyte sedimentation rate, serum electrolytes, liver function tests, serum creatinine, and creatinine clearance.

Clinical assessment

After starting C_sA, patients were seen weekly for the first month and then at least at monthly intervals for the first six months. They were examined neurologically and their degree of disability was scored.² Serum creatinine, serum electrolytes, full blood count, liver function tests, C_sA whole blood levels, and blood pressure were monitored. If the serum creatinine rose during the period of treatment creatinine clearance was performed; if the serum creatinine levels did not rise the creatinine clearance was repeated at the end of one month and again after three to six months. Nerve conduction studies were performed on all patients before starting C_sA and for most patients at six to 12 month intervals thereafter.

The experimental nature of the treatment and the potential toxicity of C_sA were explained in detail to all the patients before they gave their informed consent. The clinical trial was approved by the Medical Ethics Committee of the Royal Prince Alfred Hospital.

Dosage

C_sA was started at 10 mg/kg/day in most patients. After one month the dosage was reduced to 8 mg/kg/day and by three months to 5 mg/kg/day. If the patient remained stable or had improved it was reduced further at six months. If a relapse occurred the dose was increased to the pre-relapse level. The whole blood C_sA level was monitored using radioimmuno assay (Sandoz, Basle CH); on two occasions when the level was higher than 800 ng/ml the dose was reduced. The dose of prednisone and the frequency of plasmapheresis were left unchanged until the patient

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Table Results of cyclosporin therapy in chronic demyelinating neuropathy

Case	Sex/ age*	Course of CIDP	Para- protein	C _s A Therapy		Duration	Previous treatment	Results of C _s A therapy	Side effects of treatment
				Starting dose (mg/kg/day)	Maintenance dose (mg/kg/day)				
1	M 47	Relapsing	IgGκ	10	2	3½ years	Pred, PP	Asymptomatic. No further relapses. No therapy required	Nausea with 10 mg/kg/day dose
2	M 32	Relapsing	—	8	2	2½ years	Pred, PP, AZP	Complete remission. No therapy required	Creatinine clearance fell to 76 ml/min
3	F 58	Progressive	IgGκ	5	5	6 months	Pred, PP, AZP	PP not required for 1 year	Malaise, hirsutism
4	M 71	Progressive	IgMλ	10	3	1 year	Pred, PP, AZP	Stabilisation. PP and Pred required	Nil
5	F 30	Relapsing	IgMλ	10	5-6	3½ years	Pred, PP	Stabilisation. Pred dose, frequency of PP reduced	Nausea, oedema, hirsutism
6	F 69	Relapsing	—	15	2	2 years	Pred, CP, PP	Stabilised on reduced Pred, CP dosage	Hirsutism, oedema, reduced creatinine clearance
7	F 25	Progressive	Polyclonal IgM	11	4.5	4 years	Pred, AZP, PP. Total body irradiation	Stabilised. Reduced PP frequency	Hypertension
8	F 39	Relapsing	—	8	6	1 year	Pred, PP, AZP	No relapses, steady improvement. Reduced PP and Pred. Virtually asymptomatic	

*At start of C_sA. Pred = Prednisone; AZP = Azathioprine; PP = Plasmapheresis; CP = Cyclophosphamide.

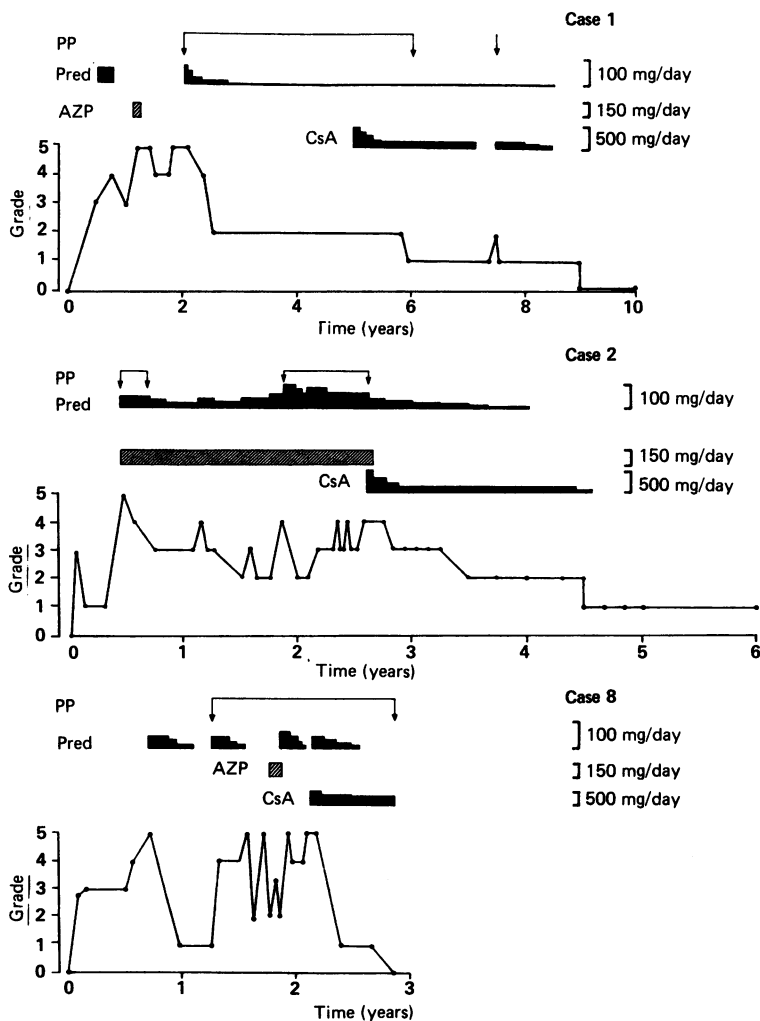


Figure Response to treatment of cases 1, 2 and 8. Arrows indicate plasmapheresis (PP). Pred = prednisone; AZP = azathioprine; C_sA = cyclosporin A. Grades of disability: 0 = normal, 1 = signs but no symptoms or vice versa, 2 = mild motor and/or sensory symptoms with signs, 3 = moderately disabled by motor and sensory symptoms including ataxia, 4 = requiring assistance with eating or dressing, or using walking aid, 5 = not ambulant.

had improved and then each was gradually reduced. Azathioprine was continued for the first week of C_sA administration and then withdrawn. If creatinine clearance was reduced to less than 50% of the baseline level or if the creatinine levels doubled C_sA dosage was discontinued if improvement had not followed reduction. If there was any deterioration of renal function the dose was reduced more rapidly. When C_sA was finally discontinued in most cases it was withdrawn slowly.

Results

The results of treatment of eight patients with C_sA are summarised in the table. Their ages ranged from 25 to 71 years. Five had a relapsing course and three had a progressive course. Five patients had a paraproteinaemia. All patients had received an adequate course of treatment with prednisone and plasmapheresis before starting C_sA. In addition, five patients had been treated with azathioprine and one with cyclophosphamide. Duration of C_sA therapy ranged from six months to four years. There were no serious side effects in any patient; creatinine clearance fell below the normal range in two patients but returned to normal after cessation of treatment. Minor side effects of nausea, oedema and hirsutism were noted in some patients. Three patients (cases 1, 2 and 8) went into complete remission following C_sA therapy, and no relapses have occurred in the two patients (cases 1, 2) whose treatment finished over one year ago. The course of the illness in these three patients is illustrated in the figure. Previously, case 3 required maintenance plasmapheresis every two to three weeks but this treatment was not necessary for a period of one year during or after C_sA therapy. The other four patients were stabilised on lower doses of corticosteroid and less frequent plasma exchanges.

Case reports

Case 1

In June 1979 this man aged 43 years developed symptoms and signs of a sensorimotor neuropathy with gradual onset and progression over

a period of one year. A clinical diagnosis of chronic demyelinating neuropathy was confirmed by electrophysiological studies and sural nerve biopsy. An IgG κ paraprotein was detected in the serum. There was an initial response to prednisone, but relapses occurred that failed to respond to treatment with corticosteroid and azathioprine therapy and he became quadriplegic. Following plasmapheresis he made a good recovery and was able to walk without assistance. Regular three weekly plasma exchanges and prednisone, 5 mg on alternate days, was necessary to prevent relapse. In June 1984 C_sA was started at a dose of 10 mg/kg/day and gradually reduced to a maintenance dose of 3–4 mg/kg/day. The interval between plasma exchanges was increased but on stopping C_sA for one month in January 1987 a relapse occurred; after a single plasma exchange and restarting C_sA 2.5 mg/kg/day and prednisone 5 mg on alternate days he became asymptomatic. From June to December 1987 the dose of C_sA was gradually reduced and finally stopped. He has remained symptom free without any treatment for 18 months. In this case treatment with C_sA has been associated with complete remission of relapsing demyelinating neuropathy. No significant improvement occurred during the first six months of the three and a half years course of treatment. The paraproteinaemia has persisted.

Case 2

In May 1983 this man aged 35 years developed diplopia; there was initial spontaneous improvement but a relapse occurred in July 1983 associated with ataxia and areflexia. In August 1983, following a viral infection, he developed a severe symmetrical sensorimotor neuropathy with ophthalmoplegia, facial diplegia and an inability to walk. Nerve conduction studies revealed gross slowing of motor conduction with conduction block and the diagnosis of CIDP was confirmed by sural nerve biopsy. Improvement followed treatment with prednisone, azathioprine and plasmapheresis but relapses occurred in October 1984 and February 1985. In spite of treatment with prednisone 50 mg/day, azathioprine 150 mg/day, and weekly plasmapheresis he remained weak. Treatment with C_sA was started initially at 8 mg/kg/day reducing gradually to a maintenance dose of 3 mg/kg/day. Azathioprine was stopped and prednisone gradually withdrawn. C_sA was stopped in December 1987. In February 1988 his condition was stable; he had only mild disability and had not required plasmapheresis nor experienced relapses for three years.

This patient, who had had frequent relapses of CIDP and was dependent on corticosteroid and immunosuppressive therapy and plasmapheresis, improved after treatment with C_sA and this was continued for two and a half years. He has remained stable without treatment for one year.

Case 8

Following a viral illness in July 1986 this 41 year old woman developed a symmetrical sensorimotor neuropathy which stabilised after

progressing for about two weeks. Relapses occurred in February and April 1987 and she was treated with prednisone 40 mg a day with resulting improvement. There was a further relapse in October 1987 when plasmapheresis was started. She was unable to tolerate azathioprine. A diagnosis of CIDP was confirmed by electrophysiological studies and sural nerve biopsy. Although she initially improved with plasma exchange, relapses in January, February and March 1988 necessitated further intensive courses of plasmapheresis. By March 1988 she was tetraparetic and unable to walk. Some improvement followed an intensive course of plasmapheresis but maintenance therapy with exchanges two to three times weekly was necessary. Despite this treatment she required walking aids. Weakness was exacerbated premenstrually. In June 1988 treatment with C_sA (8 mg/kg/day) was started together with prednisone 40 mg/day. C_sA dosage was then reduced to 6 mg/kg/day. Since introduction of C_sA there have been no further relapses and muscle power has improved considerably. She is able to walk without assistance. Prednisone has been reduced to 15 mg daily and the frequency of plasma exchanges has increased to two weekly intervals.

This patient with a relapse of CIDP that had failed to respond to intensive treatment with corticosteroids and plasma exchange improved considerably after starting C_sA. No further relapses have occurred during the six month period of treatment.

Discussion

Three patients had CIDP and five others had a chronic demyelinating neuropathy with similar clinical and pathological features, but an associated benign paraproteinaemia. In each case there was a severe disability that had not responded to treatment with corticosteroids, azathioprine and plasmapheresis. They were all having maintenance plasmapheresis at the time of starting C_sA therapy. In all cases some benefit was derived from C_sA; three patients (cases 1, 2 and 8) had an excellent response and two of these (cases 1 and 2) went into complete remission. Cases 1 and 2 were treated for periods of three and a half and two and a half years respectively and have remained in remission for more than one year since therapy has stopped. In most cases it was possible to reduce the corticosteroid dose or stop the drug altogether, and to reduce the frequency of plasmapheresis or discontinue it entirely. In two cases (cases 1 and 5) there had been a recurrence of symptoms when the C_sA dosage was reduced within the first six months of treatment, an observation that supports the therapeutic value of the C_sA treatment. There were no significant changes in the nerve conduction studies in any of the patients over the observation periods.

There were no serious side effects in any patient and none had persistent impairment of renal function.

C_sA is thought to act partly as an immunosuppressive agent by inhibiting lymphokine release (including gamma interferon and interleukin 2) and target cell responsiveness to

lymphokine, rather than by affecting cytotoxic killing mechanisms.^{14,15} Gamma interferon is a potent regulator of MHC expression and macrophage activation.^{4,16} The pathological features of CIDP suggest a delayed hypersensitivity response in which nerve damage is affected by the recruitment and activation of macrophages,¹⁷ processes that are mediated by lymphokines (including gamma interferon) released by CD4 cells.¹⁸ Such responses are initiated by the presentation of antigen (by macrophage or Schwann cell) to CD4 cells in the context of Class II MHC molecules. It is also recognised that quantitative variation is the expression of MHC products, particularly MHC Class II, is a major regulator of immune responses.¹⁹ C_sA may therefore exert its effect in CIDP through its action on lymphokine release thereby reducing MHC molecule expression and effector cell recruitment and activation.

There have been several previous reports of the use of C_sA. Gross and Thomas⁵ reported six cases of CIDP treated with plasmapheresis. Their cases 2 and 3 were also given C_sA following plasma exchange; case 2 ceased to progress or relapse after a four week course of C_sA but case 3, who had been given 17.5 mg/kg/day of C_sA, had progressive and profound deterioration following this therapy and the drug was discontinued. Kolkin *et al*²⁰ reported one patient with severe CIDP who had been treated with 7.5 mg/kg/day of C_sA for two years. After two years the blood pressure rose precipitously and she developed terminal renal failure. However, during the period of time that she was receiving C_sA her neuropathy improved considerably. It is now apparent that C_sA almost always causes some renal toxicity which, to a certain extent, is dose related.²¹ In animal experiments, King *et al*¹³ have reported that experimental allergic neuritis was suppressed by C_sA.

In our cases every effort was made to ensure that the patients were maintained on the smallest possible dose of C_sA, in some cases as low as 2–3 mg/kg/day. No patient had a lasting rise in creatinine clearance. Renal biopsy of patients given C_sA for uveitis²² have shown that some patients have interstitial fibrosis and sclerosis, even when their creatinine is normal and it is possible that some of our patients may have suffered renal damage that was not clinically evident.

It is interesting that four of our cases had monoclonal paraprotein bands (2 IgGκ, 2 IgMλ). The classification of these cases of chronic demyelinating neuropathy is uncertain, and some researchers consider the presence of a paraprotein band excludes the diagnosis of CIDP.^{23,24} In all our cases the clinical and electrophysiological features were consistent with the diagnosis of CIDP, and the sural nerve biopsy showed macrophage mediated demyelination and an active inflammatory cell infiltrate. Moreover, no immunoglobulin binding to nerve fibres was demonstrated by appropriate immunofluorescent techniques and no widening of myelin lamellae was seen by electronmicroscopy. The paraproteinaemia persisted, despite clinical improvement during

treatment with C_sA and other immunosuppressive agents.

Because all the other drugs which could be or have been used in chronic demyelinating neuropathies may have serious side effects, we believe that C_sA may be a useful adjunct to therapy in patients who have been difficult to manage with conventional therapies of prednisone, plasmapheresis and azathioprine provided that renal function is carefully monitored and the possible complications of treatment are carefully considered in relation to the natural history of the disease.³ The favourable results of this open pilot study suggest that a double blind controlled trial of C_sA in the treatment of chronic demyelinating neuropathies is warranted.

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