CYCLOSPORIN FOR THE TREATMENT OF DERMATOMYOSITIS

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ABSTRACT

2 patients with extreme severe dermatomyositis, 2 patients who were at risk because of corticosteroid side effects due to underlying diseases - and 1 patient with amyopathic dermatomyositis who was resistant to previous corticosteroid treatment were treated with 5 mg/kg/d cyclosporin A (CSP) and prednisone. CSP treatment has been shown to be beneficial in all 5 patients. CSP treatment was discontinued after 3 and 4 months in 2 of the patients with severe disease course because of renal side effects, which were reversible. In no cases were found underlying malignancies. CSP treatment seems to be a valuable second line drug in extreme severe cases of dermatomyositis, in cases who are at risk because of corticosteroid side effects, and in patients who are unresponsive to corticosteroid treatment.

KEY WORDS

cyclosporin A, dermatomyositis, renal side effects, malignancy

INTRODUCTION

Over the past years, cyclosporin A (CSP) has been used to treat a range of immunologically mediated dermatological diseases. The immunsosuppressive effects of CSP are the consequences of the inhibition of IL 2 and other lymphokine secretion by activated T cells. Its effect is established in severe chronic plaque type and pustular psoriasis (7, 8, 10, 11). Its use by dermatologists includes the treatment of psoriasis, Behcet's disease, pyoderma gangrenosum, atopic dermatitis, pemphigus vulgaris, pemphigoid bullosus, systemic lupus erythematosus, lichen planus, alopecia areata, ichthyosis (19).

There is now increasing evidence suggesting that CSP is useful in the treatment of dermatomyositis. This is a report of uncontrolled studies in 5 patients who were treated with CSP and corticosteroids.

CASE REPORTS

Case 1.

A 52-year-old man presented with a history of myalgias and weakness and a non-pruritic erythematous rash for 5 weeks. He has had insulin-dependent diabetes mellitus for 5 years, and he has been on insulin therapy. Examination

revealed violaceous plaques on his neck, forearms, chest, elbow, knee and periorbital area. Periungual erythema without teleangiectasia was noted. Baseline studies included the following determinations (in all cases): complete blood cell count, hemoglobin concentration, urinalysis, serum alkaline phosphatase, serum bilirubin, GOT, GPT, creatin kinase, lactic dehydrogenase, uric acid, total serum protein, blood glucose, serum creatinine, GFR clearance, BUN, antinuclear antibody test (on rat liver), EMG, skin and muscle biopsy. Results of laboratory findings resulted in elevated creatin kinase (normal level: below 195 u/ml,) lactic dehydrogenase (normal level: 230-460 u/ml), GPT: 50 u/ml, blood glucose 15,1 mimol/1. Results of muscle biopsy and EMG were compatible with dermatomyositis. Prednisone at 30 mg/d dose was started; because of elevation in blood glucose (19,8 mmol/1, 24,9 mml/l, 22,9 mmol/l, and aceton in urine the prednisone dosage was reduced rapidly to 20 mg/d and CSP at 5 mg/kg/dose was started. The prednisone dosage has been tapered to 14 mg/d in three weeks. CSP dosage has been subsequently tapered at monthly intervals. After 3 weeks of starting CSP treatment, muscle involvement improved. Skin symptoms seemed to be more resistant to treatment, but within 3 months of starting CSP treatment the patient showed some improvement in the extent and severity of skin involvements. Maintenance has been achieved at 1,5 mg/kg/d CSP and 7 mg/d prednisone. 11 months after starting the treatment he is in good general health but residual skin symptoms are still to be seen. No serious side effects of CSP treatment were observed.

Case 2.

A 39-year-old man presented with muscle weakness, intermittent muscle pain in his proximal thighs, and skin lesions on his face, on his chest and on his hands of one month duration. His past medical history included ulcus duodeni since 1983, haemorrhagia ventriculi approximately two years prior to admission and deep vein thrombosis 3 years prior to admission. Examination revealed periorbital heliotrope eruption, violaceous erythema of the neck, upper chest and Gottron's papules. Results of skin and muscle biopsy specimens were compatible with dermatomyositis. All laboratory tests were within normal level except elevated creatin kinase: 380 u/ml, lactic dehydrogenase: 603 u/ml and elevated serum bilirubin level: 31 mmol/l. Antinuclear antibody test was negative. An initial high dose of prednisone (125 mg/d) was followed by rapid rate tapering. After two weeks of starting the prednisone therapy additional CSP was started at 5 mg/kg/day dose. The patient began to respond within 4 weeks of treatment. CSP dosage was adjusted downward by 1 mg/kg/d at monthly intervals after an initial 1 month of therapy. Maintenance has been achieved with 1,5 mg/kg/d CSP and 15 mg prednisone every other day. 10 months after starting the therapy the patient has signs of neither skin nor muscle involvement. No serious side effects were noted. Serum bilirubin was rigorously monitored. The treatment did not cause further elevation of serum bilirubin level.

Case 3.

A 47-year-old female patient has had pruritic, widespread skin symptoms and muscle weakness with fatigue and lethargy. Erroneous initial diagnosis given our patient before seeing us were: contact dermatitis, viral infection, Lyell syndrome? She came to our clinic with severe proximal muscle weakness and pain in the shoulders, hips and thighs. She had severe dysphagia and respiratory muscle involvement. She had widespread violaceous erythematous papules and plaques on her neck, back, chest, on back of her hands, on elbows, shoulders, buttocks, thighs and extensor arms, on some areas with subepidermal bullas and erosions. She had violaceous erythema on the face and scalp, including periorbital edema. Creatin kinase level was highly elevated, 2560 u/ml, lactic dehydrogenase 1309 u/ml, GOT 108 u/ml, blood sugar 10,8 mmol/l. Antinuclear antibody test was negative. Intravenous pulse steroid (1 g/d) was started as her lesions required urgent treatment. After 5 days when tapering the corticosteroid dose to 125 mg/d, CSP therapy was started, followed by monthly tapering. After 1 month of therapy moderate improvement was seen, creatin kinase was 258 u/ml, lactic dehydrogenase 892 u/ml. After 2 months of therapy there was a marked improvement (creatin kinase 46 u/ml, lactic dehydrogenase 731 u/ml) both in skin and muscle involvement. 4 months after starting CSP serum creatinine levels rose to more than 30 % over baseline values. The dose was therefore reduced to 1,5 mg/kg/d, but the serum creatinine levels did not decrease so the CSP treatment was stopped. The patient was subsequently controlled with prednisone. After 9 months after the start of the disease the patient had no skin disease, moderate muscle weakness and takes 30 mg prednisone daily. Her serum creatinine decreased to normal level.

Case 4.

This 45-year-old female patient presented with a 2-year history of dermatomyositis that had been previously treated with corticosteroids. 3 months before admission the patient stopped the treatment with no other medication and developed a recurrence. Examination revealed violaceous erythema of the face, violaceous plaques on chest, on thighs, on arms with bulla formation, Gottron's papules, periungual teleangiectasia and erythema. There was severe proximal muscle weakness. Results of laboratory tests included increased creatin kinase level: 9530 u/ml, increased lactic dehydrogenase level: 1510 u/ml, increased GPT level: 141 u/ml. Antinuclear antibody test showed speckled type reactivity at 1/160 dil. High dose prednisone 250 mg/d was started then tapering the

corticosteroid dose CSP at 5 mg/kg/d was given. After two months of treatment the patient's motor strength was much improved, muscle tenderness decreased, skin eruptions improved, dysphagia disappeared. Serum enzyme levels were as follows: creatin kinase 230 u/ml, lactic dehydrogenase 1101 u/ml, GPT 69. 3 months after starting the CSP the GFR clearance was 57 ml/min, therefore the CSP therapy was discontinued. After 11 months of this relapse she remains asymptomatic taking prednisone at a maintenance dose of 25 mg/d.

Case 5.

The 19-year-old female patient had been in good health until June 1991 when she noted discreet eruptions on the back of her hands, later extensive joint tenderness with swelling of the joints: shoulder, knee and hip, DIP. 3 months later more extensive skin symptoms started on elbows and thighs. She was admitted to a medical department. Laboratory findings revealed normal creatin kinase (40 u/ml), lactic dehydrogenase (423 u/ml) negative antinuclear antibody, anti-Sm, anti-RNP, dsDNA, Ro/SSA, La/SSB tests, normal total haemolytic complement, C3, C4 level. No classified autoimmune disease was suspected. 40 mg/d prednisone was started, later tapering the dose to 20 mg/d. Joints complaints markedly improved but skin symptoms continued to be resistant to treatment. 1 year after the start of the disease she was admitted to our clinic. Examination revealed large, hyperkeratotic violaceous plaques on elbows with ulceration and calcinosis of soft tissue. On thighs violaceous plaques, on the face heliotrope eruption with edema and Gottron's papules were seen. Muscle strength was normal. Skin biopsy was compatible with dermatomyositis. All laboratory tests - included creatin kinase and lactic dehydrogenase - were within normal limits. The diagnosis of amyopathic form of dermatomyositis was made. The corticosteroid dose was increased to 60 mg/d. Skin symptoms did not respond, therefore CSP was started at 5 mg/kg/d with reduced dose of prednisone. After 1 month of starting therapy dramatic improvement was seen both in skin and joint involvements. The CSP dose was reduced at monthly intervals. She has taken CSP at a maintenance dose of 2 mg/kg/d and prednisone at dose of 15 mg/d. for 7 months then CSP therapy was stopped. No serious side effects were seen. The patient has remained symptom-free for more than 10 months after CSP therapy was discontinued.

In two cases were found underlying malignancies.

DISCUSSION

There are several anecdotal reports on the beneficial effect of low dose CSP in dermatomyositis. Zabel reported a 15-year-old girl with extreme severe disease who was treated with CSP after prednisone and azathioprine proved to be ineffective. It was suggested that CSP treatment is justified in unusually severe cases of dermatomyositis unresponsive to conventional therapy (20). A 14-year-old boy has been successfully treated with CSP and low dose prednisone. The treatment resulted in complete remission (9). 14 patients with chronic active juvenile dermatomyositis were successfully treated with CSP. It was possible to stop steroids or reduce the steroid dose in all patients (13). Dantzig reported good response after CSP treatment of a 4 year-old girl (5). These experiences suggest that CSP may be valuable in treating juvenile dermatomyositis patients because it avoids the sequele of prolonged steroid use.

Casato and his coworkers treated an adult patient with CSP and corticosteroids who responded dramatically to the treatment (2). Danko and her coworker treated 10 patients with CSP at 5 mg/kg/d, all of whom responded to the treatment. (2 of them were unresponsive to previous corticosteroid therapy) (4). Mehregan et al successfully treated one case of dermatomyositis and one case of polymyositis/scleroderma overlap who did not respond to previous corticosteroid treatment (17).

Similarly good response was observed in cases of polymyositis. (1, 12, 16).

However there have been treatment failures. The case of Levi did not respond to 4 weeks of CSP treatment (This patient was resistant to steroids and azathioprin too) (15).

No serious side effects were observed in these cases.

In most studies CSP was administered with corticosteroids as in our cases. All five patients responded well to CSP and corticosteroid treatment. In two of our patients with extreme severe disease form (Patients Number 3, 4) CSP was added to high dose prednisone aiming to a rapid clinical control of the disease. Both patients showed dramatic improvement after 2 months of therapy. Two of our patients (Patients Number 1, 2) were at risk for corticosteroid treatment because of under-lying diseases. In them the CSP treatment enabled to control the disease with lower corticosteroid doses and we could reduce the dose more rapidly then usual in this disease. Pa-tient Number 5 who was unresponsive to previous corticosteroid therapy showed marked improvement after CSP was added to corticosteroids. The treatment was discontinued after 4 and 3 months of therapy in cases 3 and 4 because of renal side effects, which were reversible. However the early aggressive treatment with CSP and high dose of corticosteroids of these extreme severe cases resulted in rapid control of active disease.

Dermatomyositis is an illness which often responds well to early aggressive therapy with corticosteroids. Nevertheless there are cases which are resistant to treatment, or serious side effects to continue the treatment. There is no clear agreement about the use of second-line drugs such as cytotoxic agents. To broaden the additive treatment modalities seems to be

reasonable. Our experience as well as the experiences of others suggest that CSP may be valuable as a second-line drug in the therapy of dermatomyositis. We advocate adding it to corticosteroid therapy if large doses of corticosteroids fail to control the disease over a reasonable period of time, or if steroid side effects are becoming troublesome or if a more rapid onset of action is desired. To determine the exact role of CSP in dermatomyositis therapy more time and well controlled trials are needed.

In patients on CSP development of malignancies has been reported (3, 14, 18). The question arises if CSP treatment does not alter the risk of eventual late development of malignancy in dermatomyositis patients. Long-term experience and controlled studies are lacking to answer this question.

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