Treatment of severe and difficult cases of systemic lupus erythematosus with tacrolimus. A report of three cases

M Duddridge, R J Powell

Abstract

Objectives—An analysis of the efficacy of tacrolimus treatment in three patients with difficult and severe systemic lupus erythematosus (SLE) whose active disease had been previously poorly controlled by cyclosporine and cyclophosphamide.

Methods—A review of patient notes.

Results—Two patients are well controlled after six and nine months of treatment with tacrolimus 0.06 mg/kg/day and 0.18 mg/kg/day. Previous persistent vasculitis had resolved and other features of active disease were controlled. The third patient's vasculitis had not improved significantly after two months of treatment and tacrolimus 0.17 mg/kg/day was discontinued because of nephrotoxicity.

Conclusion—Tacrolimus may be a useful additional immunosuppressive agent in some patients whose SLE is not well controlled by conventional treatments.

(*Ann Rheum Dis* 1997;56:690-692)

Several groups have reported the efficacy of cyclosporine in systemic lupus erythematosus (SLE).¹⁻³ There have been no previous reports of the treatment of the connective tissue diseases with the other immunophilin ligands, such as tacrolimus or rapamycin, although tacrolimus (FK506) has been successfully used in the treatment of other autoimmune diseases.^{4,5} We report the treatment of three cases of severe and difficult SLE with tacrolimus.

Case reports

CASE ONE

A 29 year old Afro-Caribbean woman with a two year history of SLE (arthritis, leucopenia, dsDNA, ANA IgG 1:200) presented with severe cutaneous vasculitis despite treatment with oral methotrexate. There was no sustained improvement with pulse intravenous cyclophosphamide (9 g in four months) in combination with oral prednisolone (maximum dose 40 mg daily) and pulse intravenous methyl prednisolone (17 g in five months). Leucopenia (as a result of peripheral consumption) and patient compliance limited the frequency of pulse cyclophosphamide therapy. There was no clinical benefit from subsequent treatment with cyclosporine (Neoral) up to 7 mg/kg/day, with therapeutic trough drug levels being attained (recommended range 95-205 µg/l), and she continued to require pulse intravenous methyl-

prednisolone and oral prednisolone 25 mg daily to control her severe cutaneous vasculitis. In June 1996 she was given tacrolimus 0.07 mg/kg/day and the dose increased after one week to 0.11 mg/kg/day with resolution of her cutaneous vasculitis. The oral prednisolone was slowly reduced and withdrawn after two months of tacrolimus treatment. At four and five months after starting tacrolimus there were two recurrent transient episodes of digital vasculitis with no recurrence in the four months after the dose was increased to 0.18 mg/kg/day. The disease related leucopenia and hypocomplementaemia had resolved and the erythrocyte sedimentation rate had fallen from 41 mm 1st h to 14 mm 1st h after six months of treatment. The only significant side effect of tacrolimus was transient hypertension (blood pressure 160/105 mm Hg at a single visit immediately after a dose increment), which did not require treatment. The creatinine did not rise with this event and fell from 81 µmol/l before treatment with tacrolimus to 70 µmol/l after nine months of treatment with tacrolimus.

CASE TWO

An 18 year old Asian man with a three year history of SLE (arthritis, malar rash, oral ulcers, lymphopenia, dsDNA, ANA IgG 1:3200) had previously been treated with sequential azathioprine and both pulse intravenous and oral daily cyclophosphamide (32 g in eight months), with concomitant oral prednisolone (maximum dose 20 mg daily), for a severe debilitating subdermal panniculitis and cutaneous vasculitis. An episode of microbiologically unexplained diarrhoea may have been secondary to gastrointestinal cyclophosphamide toxicity and he was subsequently treated with cyclosporine (Neoral) up to 7 mg/kg/day with clinical deterioration rather than improvement. A failure of absorption of Neoral was thought to explain low/undetectable trough levels of cyclosporine. In October 1996 he was given tacrolimus 0.10 mg/kg/day after presenting with severe digital vasculitis and gangrene. In six months of follow up there has been no recurrence of his vasculitis and his arthritis remains controlled. After three months of treatment his prednisolone dose has been reduced from 30 mg daily to 10 mg daily, on which dose he has remained. His erythrocyte sedimentation rate has remained unchanged throughout (49 mm 1st h), which may be explained by intercurrent infection of a dry gangrenous finger tip. However, his urinary neopterin has fallen from 1491 µmol/mol

Clinical Immunology Unit, University Hospital, Queen's Medical Centre, Nottingham
M Duddridge
R J Powell

Correspondence to: Dr M Duddridge, Clinical Immunology Unit, F Floor West Block, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.

Accepted for publication 2 September 1997

creatinine to 366 $\mu\text{mol/mol}$ creatinine (normal range <200 $\mu\text{mol/mol}$ creatinine), probably reflecting his improved disease control.

After one month's treatment with tacrolimus he became mildly hypertensive (blood pressure 160/100 mm Hg), without a significant rise in creatinine (77 $\mu\text{mol/l}$ to 81 $\mu\text{mol/l}$), in association with 12 hour trough tacrolimus levels at the higher end of the therapeutic range (peak 20.2 $\mu\text{g/l}$; recommended range 4–25 $\mu\text{g/l}$). His hypertension responded to the combination of a reduction in the dose of tacrolimus to 0.06 mg/kg/day and introduction of an angiotensin converting enzyme inhibitor. After six months' treatment with tacrolimus his creatinine had risen by 16% from 77 $\mu\text{mol/l}$ to 92 $\mu\text{mol/l}$.

CASE THREE

A 36 year old Afro-Caribbean woman with a 15 year history of SLE (arthritis, discoid rash, photosensitivity, oral ulceration, pericarditis, ANA IgG 1:800) presented with severe cutaneous vasculitis despite treatment with oral methotrexate. This did not improve with pulse intravenous cyclophosphamide (15 g in six months), in combination with oral prednisolone (maximum dose 20 mg daily) and pulse intravenous methylprednisolone (15 g in six months), although leucopenia and gastrointestinal toxicity limited treatment with pulse cyclophosphamide. She was subsequently treated with cyclosporine (Neoral) up to 5 mg/kg/day with some improvement, but this was later withdrawn because of a reversible nephropathy (creatinine rising to 346 $\mu\text{mol/l}$), neurotoxicity, and hypertension (blood pressure 200/120 mm Hg) in association with a 12 hour trough cyclosporine level at the upper end of the therapeutic range (199 $\mu\text{g/l}$). She was given tacrolimus in November 1996 with deterioration of her vasculitis and arthritis after withdrawal of the cyclosporine treatment. The dose of tacrolimus was increased from 0.04 mg/kg/day to 0.17 mg/kg/day over a two month period without appreciable improvement in her vasculitis. The erythrocyte sedimentation rate was unchanged during the two months of treatment.

With the highest dose of tacrolimus her creatinine rose from 90 $\mu\text{mol/l}$ to 208 $\mu\text{mol/l}$ in association with a 12 hour trough tacrolimus level at the higher end of the therapeutic range (23.2 $\mu\text{g/l}$), and the tacrolimus was withdrawn. Hypertension (blood pressure 190/110 mm Hg) associated with the lowest dose of tacrolimus had been successfully treated with an angiotensin converting enzyme inhibitor, but recurred with the above episode of reversible nephrotoxicity (creatinine fell to 112 $\mu\text{mol/l}$ within seven days of stopping tacrolimus, without other change in her treatment). There was no active urinary sediment, hypocomplementaemia nor clinical features to suggest renal SLE. She was subsequently again treated with pulse intravenous cyclophosphamide with improvement, but not full control of the cutaneous vasculitis.

Discussion

Tacrolimus has not previously been described in the treatment of SLE although cyclosporine

is being increasingly used. We have described the successful treatment of two cases of SLE with tacrolimus that had previously been difficult to control with both cyclophosphamide and cyclosporine. Our third case did not significantly improve with tacrolimus and it was withdrawn as a consequence of therapeutic failure and (reversible) nephrotoxicity.

Although we have only had cause to treat three of our SLE patients with tacrolimus, the apparent success rate is similar to the 64% described in other autoimmune disease that had not previously responded to cyclosporine treatment.⁴ This suggests that tacrolimus may have a role in the treatment of those patients with SLE who have proved difficult to control with other immunosuppressive agents. Until there has been a comparison of cyclosporine with tacrolimus in these patients, we would suggest that tacrolimus is reserved for those patients who have failed to respond to cyclosporine. In our own practice cyclosporine is now used in SLE after agents such as azathioprine and methotrexate, but before cyclophosphamide in (a) young patients where there is a significant risk of infertility,⁶ and (b) those where haematological involvement is a feature of disease activity with the potential difficulty in distinguishing between recurrent disease activity and cyclophosphamide induced marrow suppression.

We would suggest starting tacrolimus at a dose of 0.10 mg/kg/day (with an equally divided dose 12 hours apart), increasing the dose to 0.15 mg/kg/day as necessary according to clinical response and 12 hour trough tacrolimus whole blood values. The suggested starting dose is a compromise between the low efficacy of tacrolimus 0.05 mg/kg/day in other autoimmune disease and the increased frequency of side effects at higher starting doses.⁴ Our third case was started with a lower initial dose of tacrolimus in the face of her previous cyclosporine induced reversible nephrotoxicity to err on the side of caution. This was probably wise in retrospect with her tacrolimus induced nephrotoxicity first becoming apparent at a dose of 0.13 mg/kg/day. Whether or not tacrolimus is contraindicated in patients who have experienced cyclosporine induced reversible nephrotoxicity is unknown, but if these patients are treated with tacrolimus we would suggest close monitoring and a low threshold of suspicion. We monitor our patients who are receiving either cyclosporine or tacrolimus one to two weeks after starting treatment or a dose increment, with two further checks at two weekly intervals before monthly review if the creatinine and blood pressure are stable with an efficacious therapeutic 12 hour trough whole blood drug level. Normotensive patients without a significant ($<30\%$) rise in creatinine and well controlled disease several (about six) months after starting treatment can probably have their drug doses monitored less frequently, but renal function should continue to be monitored on a monthly basis as late increases in creatinine can occur in the absence of dose increments.²

Tacrolimus has not yet been used to treat a patient with renal SLE. Although there may be

potential difficulty in distinguishing drug induced nephrotoxicity from active renal SLE, cyclosporine has been successfully used in the treatment of renal SLE¹⁻³ and is not contraindicated in this clinical situation. The immunophilin ligands may even eventually prove to be first line treatment for lupus nephritis given the rapid improvement in proteinuria described.³

1 Miescher PA, Favre H, Mihatsch MJ, Chatelant F, Huang YP, Zubler R. The place of cyclosporine A in the treatment of connective tissue disease. *Transplant Proc* 1988;20 (suppl 4): 224-37.

- 2 Manger K, Kalden JR, Manger B. Cyclosporin A in the treatment of systemic lupus erythematosus: results of an open clinical study. *Br J Rheumatol* 1996;35:669-75.
- 3 Caccavo D, Lagana B, Mitterhofer AP, Ferri GM, Afeltra A, Amoroso A, *et al.* Long-term treatment of systemic lupus erythematosus with cyclosporin A. *Arthritis Rheum* 1997; 40:27-35.
- 4 Mochizuki M, Masuda K, Sakane T, Ito K, Kogure M, Sugino N, *et al.* A clinical trial of FK506 in refractory uveitis. *Am J Ophthalmol* 1993;115:763-9.
- 5 Ishioka M, Ohno S, Nakamura S, Isobe K, Watanabe N, Ishigatsubo Y, *et al.* FK506 treatment of noninfectious uveitis. *Am J Ophthalmol* 1994;118:723-9.
- 6 McDermott EM, Powell RJ. Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide. *Ann Rheum Dis* 1996;55:224-9.