Published in final edited form as:

Lancet. 1999 May 22; 353(9166): 1762–1763. doi:10.1016/S0140-6736(99)01927-3.

Tacrolimus in refractory polymyositis with interstitial lung disease

Chester V Oddis, Frank C Sciurba, Kareem Abu Elmagd, and Thomas E Starzl

Department of Medicine, Divisions of Rheumatology (C V Oddis oddis@med.1.dept-med.pitt.edu), and Pulmonary Medicine, and Thomas E Starzl Transplantation Institute, University of Pittsburgh, PA 15213, USA

Anti-Jo-1 is the most frequently identified autoantibody in the idiopathic inflammatory myopathies (IIM) and patients with Jo-1 may also develop interstitial pneumonitis, arthritis, and “mechanic’s hands”. Anti-signal recognition particle (SRP) identifies a second subgroup of IIM with severe muscle weakness. Patients with either antibody have a worse outlook.¹ We assessed the effectiveness of tacrolimus in treating such patients.

Patients were eligible if they had muscle weakness, raised serum creatine kinase (CK), electromyographic and biopsy evidence of active disease, and if treatment with prednisone and at least one other concomitantly administered immunosuppressive agent had failed. Patients received oral tacrolimus (0.075 mg/kg daily) in twice daily doses to achieve a 12-h plasma trough concentration of 5–20 ng/mL. Their manual muscle strength, serum CK, functional status as determined by the disability index (DI) of the Health Assessment Questionnaire (HAQ), and daily prednisone dose were recorded as outcome measures. Eight patients (five women, age range 30–70 years), were treated. Time from disease onset to treatment with tacrolimus ranged from 9 months to almost 9 years. Six had anti-Jo-1 and two had anti-SRP autoantibodies. All had corticosteroid and methotrexate-resistant disease; four had failed azathioprine, two cyclophosphamide, one intravenous immune globulin, and one plasmapheresis.

All patients had improved muscle strength after tacrolimus and five of the six anti-Jo-1 patients regained normal strength (three within 3 months, two within 6 months). Mean CK of the six anti-Jo-1 patients decreased from 3114 IU/mL to 87 IU/mL ($p < 0.01$) and three returned to normal within 1 month. The two anti-SRP patients had a decrease in their serum CK and strength improved. Patients with the anti-Jo-1 antibody had an improved functional status (mean DI of the HAQ 0.98 to 0.48, $p < 0.005$). Mean daily prednisone dose decreased by 80% in the six anti-Jo-1-positive patients (25 mg to 5 mg, $p < 0.005$, and one patient is off prednisone). Patients have received 368 patient months of tacrolimus treatment (range, 17–74 months; mean, 46 months) and none have had a flare-up of myositis flare when their tacrolimus serum concentrations were within the therapeutic range. Suboptimum concentrations (one patient) and drug discontinuation (two patients, figure), led to flares that responded favourably to restarting tacrolimus. Extramuscular manifestations such as fever, polyarthritis, and “mechanics hands” improved with tacrolimus. Five of the six Jo-1-positive patients had radiographic evidence of diffuse parenchymal interstitial infiltrates and two required treatment with oxygen. One had stable pulmonary function tests, one worsened slightly, and three responded favourably. The mean improvement in the forced vital capacity after 12, 21, and 37 months of tacrolimus in these three patients was 0.62 L (a 22% increase). Carbon monoxide diffusion improved in two patients and total lung capacity increased an average of 15%.

Tacrolimus was well tolerated. The serum creatinine increased in all patients but dosage modification led to improvement in all but one patient who developed accelerated hypertension and worsening renal function with a creatinine of 4.1 mg/dL. Tacrolimus was stopped and muscle strength and serum CK remain normal 12 months later. Two patients developed mild

anaemia and hypertension and one experienced gynaecomastia which resolved. No patients had an opportunistic infection. Another SRP-positive patient stopped tacrolimus due to concerns over side-effects.

Only 9% (3/34) of previously reported antisynthetase antibody-positive patients responded completely to treatment.² Our six Jo-1-positive patients had a good response to tacrolimus and in five it was sustained. Despite a mean tacrolimus treatment duration of 46 months and decreasing corticosteroid doses, no patient flared during treatment. There were three disease exacerbations when tacrolimus was tapered or discontinued. The prevalence of interstitial lung disease is increased in myositis patients with antisynthetase autoantibodies, is associated with reduced survival, and was the immediate cause of mortality in 58% of all deaths related to IIM.³ Four of our five Jo-1-positive patients with interstitial lung disease are stable or have improved.

Tacrolimus has been effective in treating pyoderma gangrenosum, psoriasis, uveitis, Behçets disease, nephritic syndrome, and primary sclerosing cholangitis.⁴ It inhibits activation of CD4 + T helper cells through several calcium-associated events involved in lymphokine gene transcription and interleukin-2 and other cytokines are also inhibited.⁵ Because polymyositis is predominantly a T-cell-mediated disease, one might expect IIM patients to respond more favourably to tacrolimus than those with dermatomyositis (a B-cell mediated disease). We suggest that tacrolimus be considered and studied in the treatment of patients with severe myositis with poor prognostic autoantibodies; and patients with immunological (T-cell mediated) interstitial lung disease before they develop pulmonary fibrosis.

Acknowledgments

Supported by a grant from the Commonwealth of Pennsylvania, Department of Health.

References

1. Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific antibodies define useful homogeneous patient groups. *Medicine* 1991;70:360–374. [PubMed: 1659647]
2. Jaffe MM, Love LA, Leff RL, et al. Drug therapy of the idiopathic inflammatory myopathies: predictors of response to prednisone, azathioprine and methotrexate and a comparison of their efficacy. *Am J Med* 1993;94:379–387. [PubMed: 8386437]
3. Arsuria EL, Greenberg AS. Adverse impact of interstitial pulmonary fibrosis on prognosis in PM and DM. *Semin Arthritis Rheum* 1988;18:29–37. [PubMed: 3187543]
4. Thomson AW, Carroll PB, McCauley J, et al. FK 506: A novel immunosuppressant for treatment of autoimmune disease. *Springer Semin Immunopathol* 1992;14:323–344. [PubMed: 7686690]
5. Yocum DE. Cyclosporine, FK-506, rapamycin, and other immunomodulators. *Rheumatic Dis Clin N Am* 1996;22:133–153.

Figure 1. Response of serum CK to administration of several immunosuppressives in an anti-Jo-1 antibody-positive patient

Note decrease in serum CK in response to tacrolimus (TAC) and flare of myositis (CK increase accompanied by muscle weakness) with temporary discontinuation of drug. IVIG=intravenous immune globulin, AZA=azathioprine, MTX=methotrexate, CS=corticosteroids.