Tacrolimus rescue therapy for severe respiratory failure in the anti-synthetase syndrome

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Abstract
Interstitial lung disease (ILD) is the major determinant of morbidity and mortality in the anti-synthetase syndrome (ASS). The therapeutic efficacy of corticosteroids for the ILD component is limited; hence, additional immunosuppressive and immunomodulatory therapies have been tried with a modicum of success in recent years. Tacrolimus, a calcineurin inhibitor, is one potential therapy. We describe four consecutive patients with ASS whom we treated with tacrolimus at a quaternary referral hospital in 2009–2013. All four patients had significant ILD, three had severe and progressive ILD, and two had been referred for consideration of lung transplantation. Tacrolimus use was associated with improvement in ILD in all four patients with a mean follow-up of 3 years. Our case series adds further evidence to support the use of tacrolimus as salvage therapy for severe respiratory failure due to ILD in ASS, which may be associated with a dramatic and enduring response.

Introduction
Interstitial lung disease (ILD) is the major determinant of morbidity and mortality in the anti-synthetase syndrome (ASS). Corticosteroids have been the mainstay of therapy; however, their efficacy is limited for ILD. Hence, additional immunosuppressive and immunomodulatory therapies have been proposed in small series. Tacrolimus, a calcineurin inhibitor, is one such therapy. We describe four consecutive patients with ASS whom we treated with tacrolimus at a quaternary referral hospital.

Case Report
Four patients with ASS with severe ILD were treated with tacrolimus at the Department of Thoracic Medicine and Lung Transplantation, St. Vincent’s Hospital in 2009–2013. The diagnosis of ASS was based on (1) the presence of serum antibodies against an aminoacyl tRNA synthetase; (2) the presence of ILD; and (3) the exclusion of other causes (including other systemic connective tissue diseases). All of the patients were anti-Jo1 antibody positive.

All four patients had significant ILD (see Table 1 for patient characteristics and treatment and Table 2 for pulmonary function tests). Three patients had severe and progressive ILD of whom two had been referred for consideration of lung transplantation. All four patients had been treated with oral prednisolone at high doses (50 mg/day) prior to being diagnosed with ASS and were commenced on tacrolimus, targeting a concentration at 0 h post-dose (C0) of 5–10. One patient had been treated with azathioprine in addition to prednisolone prior to the diagnosis of ASS, and another had been treated with cyclophosphamide in addition to prednisolone. Following commencement of tacrolimus, all patients were maintained on dual therapy only (tacrolimus and prednisolone). Prednisolone was continued at 50 mg/day at the start of tacrolimus therapy and subsequently weaned to the lowest dose possible to maintain symptom control. Bactrim prophylaxis was used due to high doses of corticosteroids being given. In all four patients, prednisolone was weaned to a much lower dose (see Table 1). In keeping with the diagnosis of ILD, patients had a restrictive deficit on pulmonary function testing prior to commencement on tacrolimus. All four patients have demonstrated a >10% improvement in lung function.
parameters over their course of treatment. Two of the four patients had a significant elevation of creatinine kinase (CK) prior to commencing tacrolimus, and the third patient had a marginally elevated CK at diagnosis. The fourth had a normal CK. All patients demonstrated complete normalization of CK following treatment with tacrolimus (see Table 1). Patients with significantly elevated CK levels had demonstrable muscle weakness on strength testing. Patient 1 was wheelchair bound on initial assessment. Both these patients demonstrated almost complete return to normal strength following treatment with tacrolimus associated with normalization of CK levels.

Treatment was well tolerated. The main side effects were hypertension and diabetes mellitus. Patient 1 developed diabetes mellitus and hypertension, both of which were well controlled with oral medication. Patient 2 gained a significant amount of weight. Patient 3 has not experienced any significant adverse effects, and patient 4 developed hyperglycemia since starting tacrolimus.

**Discussion**

Optimal treatment for ILD associated with polymyositis-dermatomyositis (PM-DM) is yet to be established [1]. The mainstay of therapy has been high-dose corticosteroids [2, 3]; however, efficacy is limited and additional immunosuppressive therapy is often tried [1]. Tacrolimus is a novel therapy that has been used recently in the treatment of ASS in an attempt to provide an alternative to prolonged high-dose corticosteroids with attendant morbidities and to improve response rates. Although there is yet to be a large randomized controlled trial in ASS, small case series have proved promising. In a study of 13 patients with ASS-associated ILD by Wilkes et al., all patients demonstrated a significant improvement in pulmonary function parameters after commencing treatment with tacrolimus [3]. In keeping with the current series, in the subset of patients who had not previously responded to other immunosuppressive therapy, all patients improved following treatment with tacrolimus. In addition, and again consistent with the findings in the present case series, prednisolone doses were able to be weaned in all patients [3]. Cyclosporine (CsA), another calcineurin inhibitor, has also been trialed as a therapy for patients with PM-DM. In a case series of six patients by Qushmaq et al., CsA used as second-line (salvage) therapy resulted in an improvement in pulmonary function parameters after commencing treatment with CsA. None of these patients had previously been treated with tacrolimus [4]. In a retrospective case series of 53 people by Takada et al., a subset of five PM-DM patients who had failed on other immunosuppressants including CsA responded to tacrolimus [5]. These findings are again similar to our patients, who demonstrated a universally promising response to tacrolimus as salvage therapy. Again, the two patients in our series who had been trialed on other therapy previously all demonstrated a response to tacrolimus, and the prednisolone dose was able to be weaned in our patients. There have been no head-to-head trials comparing one drug with another in treatment of ASS [6], making it impossible to draw conclusions about which therapy (if any) is superior. However, our series does demonstrate that the two patients who had not responded to

| Patient | Age/sex | Additional prior therapy | Initial prednisolone dose (mg/day) | Current prednisolone dose (mg/day) | Current FK dose (mg/day) | Follow-up (months) |
|---------|---------|--------------------------|-----------------------------------|-----------------------------------|------------------------|------------------|
| 1       | 59/M    | Nil                      | 50                                | 15                                | 3                      | 50               |
| 2       | 35/M    | Nil                      | 50                                | 7                                 | 10                     | 51               |
| 3       | 61/F    | AZA                      | 50                                | 15                                | 4                      | 26               |
| 4       | 62/F    | CYC                      | 50                                | 15                                | 1                      | 24               |

AZA, azathioprine; CYC, cyclophosphamide; FK, tacrolimus.

| Patient | FEV1 | FVC | TLC | KCO |
|---------|------|-----|-----|-----|
| Patient 1 | 0.80 | 0.84 | 2.53 | 3.08 |
| Patient 2 | 1.58 | 2.12 | 2.98 | 4.09 |
| Patient 3 | 2.23 | 3.09 | 3.91 | 5.32 |
| Patient 4 | 3.10 | 4.11 | 5.13 | 4.66 |

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; KCO, diffusing capacity of lung per unit volume; TLC, total lung capacity.

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other immunosuppressive therapy showed dramatic and sustained improvement on tacrolimus therapy. In conclusion, the present case series suggests that tacrolimus is an effective and safe treatment for ASS. Side effects are predictable and tolerable with therapy. Randomized controlled studies are needed to further assess the effect of tacrolimus on this condition and to compare the various immunosuppressive therapies available to optimize treatment of this condition, but the rarity of this disease makes it unlikely that any center will be able to conduct an adequately powered study.

**Disclosure Statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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