This editorial refers to The efficacy of tacrolimus in patients with interstitial lung disease complicated with polymyositis or dermatomyositis, by Takashi Kurita et al., doi: 10.1093/rheumatology/keu166, pages 39–44.

In this issue of Rheumatology, Kurita et al. [1] assess the effect of tacrolimus in patients with interstitial lung disease (ILD) and idiopathic inflammatory myopathy (IIM). Long-term survival in IIM has improved over the last 20 years but remains relatively poor. Ten-year survival in the UK is ~90%, comparable with SLE [2]. ILD, which occurs in ~30% of IIM cases, is a major predictor of death, yet none of the randomized controlled trials (RCTs) in IIM have included ILD-specific endpoints [3].

Treatment for IIM-associated ILD has therefore been based on case series and extrapolation from related conditions, such as SSC-associated ILD. However, the patterns of ILD associated with different autoimmune inflammatory conditions, though overlapping, do differ [4]. In addition, it is unclear whether patterns of ILD will respond identically to the same treatments in different CTDs.

The calcineurin antagonist ciclosporin has been used in IIM for some time. RCT data in adult IIM have not demonstrated efficacy, but a recent open-label RCT in JDM suggested benefit, albeit at the cost of a significant side-effect profile [3, 5, 6]. This side-effect profile has limited its use in both IIM and RA. Tacrolimus, a newer calcineurin inhibitor, has increasingly been used in myositis, particularly in the context of ILD. However, the evidence base for its use has been limited to small case series and expert opinion [7].

The retrospective study reported in this issue [1] examines the experience from 49 patients with IIM and ILD in Japan and compares outcomes between those treated with and without tacrolimus. Outcome events were defined as death, relapse of respiratory cause or severe adverse event. The 25 patients treated with tacrolimus appeared to have more severe disease than those who did not receive this treatment [1]. They had significantly higher levels of the Krebs-Von den Lungen 6 (KL-6) biomarker of ILD severity and activity and trended towards significantly lower predicted forced vital capacity (77.9% vs 85.8%, P = 0.091) and diffusing capacity for carbon monoxide (53.2% vs 64.7%, P = 0.063). To adjust for selection bias in the treatment arm, multiple severity factors were assessed and inverse probability of treatment weighting was applied. After (but not before) this adjustment, the study demonstrated significantly longer event-free survival in tacrolimus-treated patients compared with those treated with standard care [hazard ratio 0.32 (95% CI 0.14, 0.75), P = 0.008].

The study has obvious limitations: it was non-randomized, open, retrospective and relied on statistical modelling to adjust for intergroup differences. However, its endpoints, though composite, were clinically relevant and included important conclusions. Given the paucity of data in this area, it represents an important addition to the current literature. It provides some reassurance for the use of tacrolimus in moderate to severe IIM-associated ILD and sets the scene for future prospective studies. Such work may benefit from the systematic incorporation of autoantibody profile data. These can predict phenotype, outcome and response to therapy in IIM. For example, in the Rituximab in Myositis study, the largest RCT in IIM to date, anti-Jo-1 and Mi-2 antibodies predicted a shorter time to rituximab response [8].

The study was performed in Japan [1], where the incidence of anti-MDA-5-positive disease is as high as 40% in IIM-associated ILD [9]. In Japanese populations, anti-MDA-5 antibodies (previously known as anti-CADM 140) are associated with rapidly progressive ILD and clinically amyopathic DM [9]. In fact, there are data to suggest that MDA-5 antibodies may be the main predictor of mortality in a Japanese IIM-associated ILD population [9]. Thus, although antibody profiles other than anti-Jo-1 are not recorded in the study [1], anti-MDA-5 disease is likely to represent a significant proportion of the cohort. Anti-MDA-5 antibody-associated IIM is thought to occur less frequently in Caucasian populations with less aggressive ILD [10]. As such, it is not clear to what extent the results of this study [1] are applicable in non-Japanese IIM-associated ILD populations.

The stratification of ILD associated with rheumatological disease by the relevant autoimmune inflammatory condition, when following natural history and treatment response, is based on the hypothesis that differences in disease mechanism may affect them. In future studies of IIM-associated ILD, it would therefore be logical to incorporate as complete a serotypic characterization as possible, including a panel of myositis-specific antibodies. Since IIM is itself relatively rare, it may currently be overambitious to plan clinical trials of sufficient power to robustly distinguish responses between different serological subphenotypes of IIM-associated ILD. However, not only do specific serotypes correlate with
disease progression, but such characterization would also help in applying findings to non-study populations. Assessing treatment response by lung function and KL-6 levels may also improve study sensitivity and interpretation.

In summary, while the data are encouraging [1], retrospective findings dependent on statistical adjustment must be viewed with caution. Previous experience counsels that follow-up prospective studies can produce disappointment. Nonetheless, at the very least, this study [1] provides sufficient data to warrant a prospective RCT of tacrolimus in IIM-associated ILD.

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**References**


