Squamous Cell Carcinomas in 2 Patients with Diffuse Scleroderma Treated with Mycophenolate Mofetil

To the Editor:

Systemic sclerosis (SSc) is a rare multisystem connective tissue disease of unclear etiology in which vascular dysfunction, fibrosis of the skin and internal organs, and autoimmunity occur. Until recently, few treatments have been successful at reducing mortality associated with the disease. The use of angiotensin-converting enzyme (ACE) inhibitors and targeted therapies such as endothelin receptor antagonists, prostacyclins, and PDE5 inhibitors have improved outcomes with respect to renal crisis and pulmonary hypertension, respectively. However, given the natural history of the disease, treatment of severe SSc is problematic. Physicians treating SSc are torn between the principles “do no harm” and “doing good,” largely the latter in many SSc treatments that lack randomized controlled trial data.

The mechanism of immune dysregulation is not entirely clear, although it seems to play a pivotal role in disease progression. Activated T2-helper lymphocytes producing fibrogenic interleukin 4 (IL-4) and IL-13 are thought to contribute. In addition, it has been shown that early in the course of disease, activation of B cells causes fibroblasts to adopt a profibrotic phenotype via the production of antibodies. Also, activated macrophages in perivascular infiltrates produce specific chemokines, transforming growth factor- β , and platelet-derived growth factor, all thought to play a role in fibrosis^{1,2}. Given that altered immune function is thought to contribute to disease progression, several immunosuppressive regimens have been explored as possible treatment options.

Some investigators have reported on the mechanism of immune regulation with mycophenolate mofetil (MMF). Via its metabolite mycophenolic acid (MPA), MMF interferes with the metabolic pathway of *de novo* purine synthesis through inhibition of inosine monophosphate dehydrogenase, suppressing both B and T lymphocyte proliferation³. MMF is currently indicated as prophylaxis against allogeneic cardiac, renal, or hepatic transplant rejection. MMF use in transplants gives fewer malignancies than other transplant medications^{4,5}. Also, ultraviolet-B-induced skin cancer in mice, including squamous-cell carcinoma (SCC), was not increased with MMF versus placebo⁶. The risks and benefits of its use in SSc are unknown. In a retrospective analysis of 109 patients with diffuse SSc treated with MMF, Nihtyanova, *et al* report lower mortality and less pulmonary fibrosis in patients treated with MMF compared to 63 controls. When treated with an average MMF dose of 2 g daily, the 5-year survival of the MMF cohort was 95.4% compared to 85.7% in the actively treated controls ($p = 0.027$). However, little difference was seen in skin changes (as measured by modified Rodnan skin score) or lung function [as measured by forced vital capacity (FVC)] between the 2 groups⁷. Five SSc patients with new-onset SSc lung disease treated with MMF had improved lung function as measured by diffusing capacity (DLCO) and FVC after 4 to 6 months⁸. One year of MMF treatment after induction therapy with antithymocyte globulin seemed to improve skin score; however, no significant change was found in EuroQol, global health, or functional assessment measures in 13 patients⁹. In most patients, MMF was tolerated quite well, with gastrointestinal symptoms and infection being the most common side effects. However, some studies have yielded negative results. When using MMF as a longterm immunosuppressant following treatment with intravenous cyclophosphamide in patients with SSc and interstitial lung disease (ILD), no significant difference was found in FVC or DLCO in 7 patients when compared to a control group¹⁰. ILD occurs in 60%–100% of patients with SSc and represents a major cause of morbidity and mortality. Studies have shown an increase in relative risk of 5.9 (95% CI 3.05–10.31) for the development of lung cancer in patients with SSc, most commonly in patients with coexisting ILD¹¹. Other cancers may also be increased in SSc¹².

Given the lack of established evidence-based treatment in diffuse SSc, clinicians need to balance the risks and benefits of unproven treatments (such as MMF) when treating patients. We describe 2 cases that illustrate this clinical dilemma.

A 50-year-old woman had a long history of diffuse SSc diagnosed in 1980. Between 1985 and 2006 she had 2 renal transplants (the first for SSc renal crisis and the second for chronic allograft nephropathy), and was maintained receiving MMF, tacrolimus, and prednisone. During this time her SSc was stable and she was minimally symptomatic. In 2006, she developed an anorectal squamous-cell cancer, which was subsequently resected. As a result of developing the malignancy, tacrolimus was stopped in February 2006. In July 2006, she developed tightening skin and morning stiffness, consistent with a flare of SSc. In response, her prednisone was increased from 5 mg to 10 mg and while her skin symptoms improved, her renal function deteriorated, with a rise in creatinine from 123 to 172 $\mu\text{mol/l}$ and an increase in blood pressure from 125/80 to 165/95 mm Hg. SSc renal crisis was suspected, so an ACE inhibitor was added, and her prednisone was decreased to the level of her usual dose of 5 mg OD. She was thought to have an aggravation of SSc due to stopping some immunosuppression and increasing the prednisone. In consideration of her previous malignancy and requirement for transplant rejection prophylaxis, in February 2007 her immunosuppressive regimen was altered from prednisone and MMF to prednisone and sirolimus, given that there are fewer reports of skin malignancies in patients taking sirolimus. Unfortunately, weeks after her regimen was altered, a small irregular perianal lesion was identified, which was pathologically identified as extensive Bowenoid dysplasia and squamous-cell carcinoma in situ. Currently, she is being maintained on a regimen of prednisone, sirolimus, and enalapril. It was thought that her increased malignancy risk was from immunosuppression and possibly specifically MMF. Her SSc is now stable, with normal blood pressure.

The increased incidence of malignancy in the transplant population is well documented. The risk of oncogenesis is thought to correlate with extent of exposure to immunosuppression, although MMF has been reported to be associated with the lower incidence of malignancy compared to other regimens. After primary kidney transplant, MMF was found to be associated with the largest decrease in relative risk for the development of post-transplant lymphoproliferative disorder¹³. However, Wang, *et al*⁴ report no statistical difference in the development of skin malignancy with MMF compared to azathioprine after renal transplant, even though a significant decrease in relative risk was seen for patients taking 3 mg/day MMF compared to those taking 2 mg/day⁴. Interestingly, given the association between ultraviolet-induced SCC and immunosuppressive therapies, Duncan, *et al* found no difference in tumor number or size in ultraviolet-B-exposed mice treated with MMF compared to placebo⁶. Also, given the large number of different immunosuppressive drugs this patient was receiving, with recurrence when she was no longer taking MMF and was receiving sirolimus, one cannot determine the exact role (if any) of MMF in SCC in this patient.

A second patient, a 54-year-old man, had diffuse SSc that was rapidly progressive, with onset in 2001. In October 2003, he was admitted to hospital in renal crisis, with creatinine 248 $\mu\text{mol/l}$, blood pressure 180/100 mm Hg, and retinal hemorrhage. Given his ongoing active and progressive disease, he was given MMF 500 mg bid. Over the next several months, his condition remained stable on a medication regimen of MMF and ramipril. His skin score and tendon friction rubs remained unchanged. In January 2005, he first noted a persistent lesion below his left clavicle (which he did not often expose to the sun, and he was not of fair complexion or of Irish descent). In April 2005, the lesion was biopsied and characterized as a well differentiated SCC (not keratoacanthoma). He was next seen in rheumatology clinic in September 2005, when the lesion was erythematous and ulcerating and 10 $\times$ 15 cm in size. His plastic surgeon thought it was going to be a very difficult resection, with need for grafting, so he was referred to our university affiliated tertiary center; at this time his MMF was discontinued. He was seen by plastic surgery 5 weeks after ceasing treatment with MMF (having had no other prior treatment for the malignancy). Currently, the SCC under his left clavicle has completely disappeared, leaving a small residual healing area measuring 2 $\times$ 2 mm. In followup 3 months later, the skin had healed and no new lesions were identified. Although a dramatic

result was seen with respect to the malignancy, the patient did describe a subjective deterioration of his SSc with cessation of MMF. However, his skin score and tendon friction rubs had not worsened further when he was no longer taking MMF, so there was no objective evidence of efficacy or worsening with the use and discontinuation of MMF.

Although not always consistent in the literature, SSc can be associated with increased malignancies¹². There are also descriptions of SSc-associated ILD with fibrotic “scar” cancers (squamous-cell cancer)¹⁴. Without randomized controlled trials (RCT), it is difficult to interpret the risks and benefits of treating SSc with MMF. Ultimately, RCT will assist in clarifying the role of MMF (if any) in treating SSc. The potential risks and benefits in the treatment of SSc with immunosuppressives such as MMF need to be better understood. We cannot demonstrate cause and effect in the first patient — she had been exposed to multiple immunosuppressives, cancers are increased in the transplant population, and her cancer recurred while she underwent other treatment. However, the second case is suggestive, as the cancer totally regressed after removal of MMF. These cases demonstrate the difficulties of trying to determine cause and effect relationships in the treatment of SSc.

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