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

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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. 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 proliferation. 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. Also, ultraviolet-B-induced skin cancer in mice, including squamous-cell carcinoma (SCC), was not increased with MMF versus placebo. The risks and benefits of its use in SSc are unknown. In a retrospective analysis of 109 patients with diffuse SSc treated with MMF, Nhtyanova, et al reported 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 groups. 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 months. 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 patients. 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 long-term 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 group. 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 ILD. Other cancers may also be increased in SSc.

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.
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 malignancies. There are also descriptions of SSc-associated ILD with fibrotic “scar” cancers (squamous-cell cancer). 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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