Letter to the Editor

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Authors' Reply

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We thank Dr. Medford for his valuable and interesting comments [1] on our recent article in *Respiration* on mycophenolate mofetil (MMF) in the treatment of chronic pulmonary sarcoidosis [2]. He raises concerns over the development of bronchiectasis as a potential side effect of MMF. We would like to give additional data on observations in our patients and comment on his suggested strategy to be vigilant for the clinical signs of possible bronchiectasis and to check immunoglobulins (IG) in all patients when using MMF.

The development of bronchiectasis in association with the use of MMF is a rare finding, but it has been reported in case series of patients after solid organ transplantation, mainly in kidney transplant recipients [3–5]. The underlying pathophysiological mechanism for the development of bronchiectasis in these cases is still unknown, but it appears to be more likely that bronchiectasis is indirectly triggered by a strong MMF-induced humoral immunosuppression due to the inhibition of T and B cell proliferation and direct effects on IG production [6, 7] facilitating severe or recurrent infections than by a direct effect of the medication on the bronchial wall epithelium.

However, patients with pulmonary sarcoidosis or other interstitial lung diseases differ from transplant recipients with healthy lungs as bronchiectasis per se is a common feature of these pulmonary diseases, especially in chronic and advanced cases. The formation of bronchiectasis in patients with chronic pulmonary diseases is complex and can be triggered by different pathophysiological mechanisms complicating a root-cause analysis. Bronchiectasis can be caused directly by inflammatory bronchial wall damage due to the sarcoid inflammation as well as by severe or recurrent infections related to an altered immune response. The latter can either be caused by inflammatory lung disease itself or an immunosuppressive treatment. Furthermore, traction bronchiectasis can occur as a result of progressive interstitial fibrosis [8]. In our cohort, 4 patients presented with pre-existent bronchiectasis at baseline, mainly traction bronchiectasis, that remained unchanged during the observation period. None of our patients newly developed bronchiectasis or had chronic sputum production during MMF treatment. Interestingly, 1 patient developed traction bronchiectasis in a treatment-free interval 8 months after the termination of MMF treatment.

With respect to Dr. Medford's suggestion to be vigilant for signs of bronchiectasis, we would like to point out that respiratory symptoms are frequent in primary lung disease and symptoms of bronchiectasis, e.g. cough, sputum production, dyspnoea and fatigue, are not specific for bronchiectasis in the presence of pulmonary sarcoidosis or another interstitial lung disease. Nevertheless, we strongly agree that the occurrence or worsening of any of these symptoms during MMF treatment should imperatively alert the treating clinicians and result in further examinations, irrespective of the treatment indication.

MMF treatment necessitates close monitoring to ensure safety and avoid under- or overimmunosuppression. We adjusted MMF dosage on the basis of clinical symptoms, leucocyte count and MMF trough levels using a routine concentration control strategy. IG levels were not assessed routinely and measured in only 1 patient. Indeed, the patient developed hypogammaglobulinaemia, but there was no association with infections or progression of pre-existing bronchiectasis, and it did not have an impact on the MMF treatment strategy. Additionally, a detailed assessment of respiratory symptoms, lung function tests and radiographic chest examinations are part of the routine follow-up of patients with chronic pulmonary sarcoidosis, which might not be the case in patients with other indications for MMF treatment. The incidence of clinically relevant pulmonary infections was very low in our patients: there were no severe chest infections and only 2 patients required antibiotic treatment. This is in line with case series assessing MMF in the treatment of extrapulmonary sarcoidosis or interstitial lung disease associated with connective tissue disease [9–11].

The suggested formal assessment of IG levels as part of the routine monitoring strategy of all patients treated with MMF might help to identify patients at risk of respiratory infections, if IG levels are low, but it has to be considered that even normal IG levels during MMF treatment do not necessarily reflect a sufficient local immune response or always prevent the development of bronchiectasis [3], particularly if a combined immunosuppressive regimen is applied. In addition, there is no consensus on if, when and how the measured IG levels should then influence the MMF treatment strategy, or even result in an IG replacement treatment.

With the low incidence of clinically relevant pulmonary infections and in the absence of newly developed bronchiectasis in our small cohort of patients, we cannot help to clarify a possible mechanism of developing bronchiectasis in association with MMF, but we could show that MMF treatment and monitoring was safe despite the lack of IG assessment. However, the rare but significant phenomenon of developing bronchiectasis associated with MMF treatment is not yet fully explained and a formal assessment of IG levels might help to understand it. To gain more meaningful results, this should ideally be done within the setting of a well-designed prospective trial in patients without primary lung disease, which will result in less potential confounders.

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