

# Macitentan for the treatment of severe digital ulcers in a patient with mixed connective tissue disease: avoiding drug interactions

Sirs,

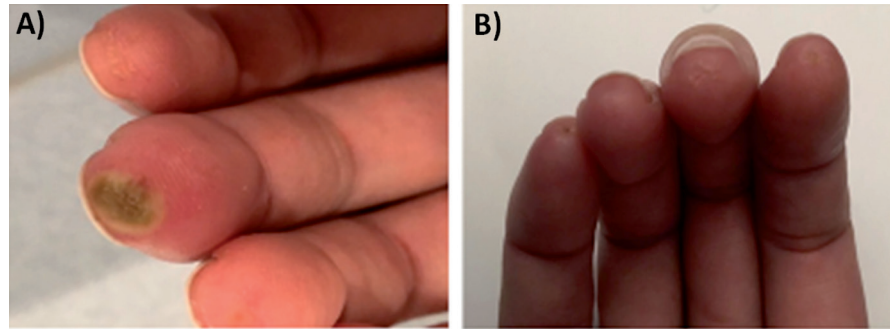
Mixed connective tissue disease (MCTD) is a systemic autoimmune disease characterized by polyarthritis, Raynaud's phenomenon (RP), lung diseases or puffy fingers (1). Treatment of MCTD is a complex process due to the high heterogeneity of clinical manifestations, the need for polypharmacy and risk of toxicity, and drug interactions. Here, we report a case of a 39-year-old woman that has been followed up by our department since she was 21 years old, diagnosed with MCTD, following Alarcón-Segovia (2) and Sharp (3) diagnostic criteria, and antiphospholipid syndrome. She presented RP, myositis, serositis, oesophageal affection, and moderate interstitial lung disease. On several occasions, she had suffered from moderate vasospasm episodes in both hands with development of digital ulcers (DU). Therefore, she was started on treatment with bosentan, which prevented the occurrence of new DU.

During the follow-up, several immunosuppressives were administered, as none of the drugs achieved a complete clinical or biological remission of the disease, and multiple side effects appeared. She reported haematological toxicity caused by azathioprine, hypersensitivity reactions during rituximab perfusion, and mycophenolate mofetil-related enterocolitis.

Given her history of drug toxicities and lung and muscle involvement, she started treatment with tacrolimus (2.5–3.0 mg/day in two divided doses) and low-dose corticosteroids (<10 mg/day), which improved muscle and lung involvement without achieving complete clinical or biological remission. Thus, cyclophosphamide administered as bolus was added to the therapy. Despite a good management of DU, treatment with bosentan was discontinued after risk/benefit assessment due to its interaction with tacrolimus.

Nevertheless, a few weeks later, she developed intense RP and severe DU, so vasodilator alprostadil was administered for 21 days, and compassionate use of macitentan, added to tacrolimus, was approved for DU prevention. After six months of treatment, she had not developed new DU (Fig. 1) and did not present relevant side effects. Finally, after one year, she did not require further treatment with alprostadil.

Different pathogenic mechanisms are involved in MCTD, so the use of different therapeutic lines are necessary for an optimal control of the symptoms. Although several immunosuppressive drugs have been used to try to modify the course of



**Fig. 1.** Digital ulcers before treatment (A) and six months after prophylaxis with macitentan (B).

interstitial lung disease, only cyclophosphamide and mycophenolate mofetil have shown some ability to slow the progression of lung injury (4,5). However, the patient received tacrolimus before cyclophosphamide because she was a young woman with gestational desire.

Bosentan is a potent dual endothelin-1 antagonist, with a proven efficacy in reducing the number, duration and severity of RP crises, and in preventing DU in patients with secondary RP associated with connective tissue diseases, being the only approved drug for such use today (6). Nevertheless, coadministration of bosentan and tacrolimus may lead to a higher reduction in plasma levels of tacrolimus, reducing its therapeutic activity and increasing plasma levels of bosentan, which may suppose an increased risk of hepatotoxicity.

Macitentan is a new dual endothelin-1 receptor antagonist indicated for the treatment of pulmonary arterial hypertension, which has been developed from a structural modification of bosentan (7). Unlike bosentan, macitentan does not interfere with hepatocyte canalicular bile salt-export pump, which avoids a toxic effect on the liver (8). In this scenario, although macitentan is not indicated for the prevention of new DU, but considering a similarity in pharmacological mechanism to bosentan (9), the low incidence of hepatotoxicity and the absence of an established interaction with calcineurin inhibitors, it was administered to the patient with good control of DU.

This case suggests that patients with MCTD or systemic sclerosis that presents RP and severe ischaemic DU may benefit from macitentan because it has fewer drug interactions and could show a similar efficacy to bosentan in controlling RP and preventing new DU.

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