

## Effect of ambrisentan on digital ulcers in systemic sclerosis: a case report

Sirs,

We present the case of a 72-year-old man with systemic sclerosis (SSc) complicated by pulmonary arterial hypertension (PAH) and skin manifestations, whose digital ulcers (DUs) were successfully treated with off-label ambrisentan therapy. His medical history included Raynaud's phenomenon (RP) diagnosed in 1988, bilateral saphenectomy for chronic venous insufficiency and arterial hypertension without other major cardiovascular risk factors. In 2002, a definitive diagnosis of SSc was made on the basis of anti-nuclear (>1:640) and anticentromere B antibodies (1.85 U/ml) positivity and active capillaroscopic pattern. His DUs were first observed in 2005, though limited to the first, second and third digits of the left foot. The patient underwent echo-Doppler of the lower limbs, with a picture of chronic venous insufficiency in the absence of arterial stenosis. He was being treated at another hospital where he started therapy with nifedipine slow release 30 mg twice daily and bosentan 62.5 mg twice daily for the first month, followed by 125 mg twice daily, which was discontinued after two months due to a significant increase in transaminase levels. Subsequently, he was treated with intravenous iloprost at the maximum tolerated dose once monthly, but the DUs did not heal. In May 2011, the patient came to our observation complaining of dyspnoea on exertion. He also continued to present DUs characterised by irregular borders, oedema, inflammation of perilesional skin and fibrin in the lesion (Fig. 1a). He underwent diagnostic work-up for PAH. Echocardiography revealed severe pulmonary hypertension, confirmed by right heart catheterisation (cardiac index 1.92 l/m<sup>2</sup>/m<sup>2</sup> BSA; mean pulmonary arterial pressure 38 cmH<sub>2</sub>O; pulmonary arterial resistance (8.45 HRU), with a negative vasoreactivity test performed by intravenous epoprostenol. Our patient was in WHO class III, and began therapy with warfarin and ambrisentan 5 mg daily, on-label for PAH associated with connective tissue diseases, including systemic sclerosis. After only 3 months of well-tolerated ambrisentan therapy the DUs healed completely (Fig. 1 b-c). However, functional status assessment with Raynaud's Condition Score (RCS) showed no improvement with the currently administered therapy. His clinical condition, as evaluated by a 6-minute walk test, cardiopulmonary test, echocardiography, BNP/NT-proBNP plasma levels, and by switching from WHO-FC III to II was deemed stable and satisfactory.

SSc is a multisystem, autoimmune connective tissue disease, characterised by vasculopathy, diffuse fibrosis of the skin and various internal organs, and immune abnormali-



**Fig. 1.** Digital ulcers before (a), at 1 month (b) and 2 months (c) after starting ambrisentan.

ties (1). RP is a cardinal feature of SSc. DUs are a common clinical problem in patients with limited or diffuse SSc, and occur in 30% and 58% of patients, respectively (2, 3). SSc-RP is the result of a vasospastic event and a structural vessel wall abnormality. Associated structural vasculopathy together with intermittent vasospasm is responsible for the severe digital vascular complications of SSc, including digital ulceration, soft tissue or bone infection, and critical ischaemia or gangrene. Endothelial injury is accompanied by increased levels of transforming growth factor-beta, connective tissue growth factor, platelet derived growth factor and endothelin-1 (ET-1), favouring fibroblast proliferation (4). The ET-1 stimulation of endothelin type A (ETA) receptors expressed on mesenchymal cells, such as smooth-muscle cells and fibroblasts, results in vasoconstriction and vascular remodelling (5). Prostacyclin analogues are the first-line therapy in the treatment of SSc-related DUs (6). Oral endothelin receptor blockers can prevent new DUs, and currently the only randomised clinical trial in the treatment of DUs is limited to bosentan (7).

Ambrisentan, a selective blocker of the ETA receptor, has proven to be effective in SSc-PAH. Preliminary data from a prospective open-label, single-centre study enrolling 20 patients with DUs secondary to SSc treated with ambrisentan revealed the efficacy of this drug in healing DUs (8). A recent study on six SSc patients with DUs and without PAH suggested that ambrisentan might be useful in the treatment of DUs in the case of previous failure of bosentan therapy (9). There is also a case report concerning the use of sitaxentan, a selective ETA receptor antagonist for the treatment of DUs, with complete healing of DUs after four months (10). Sitaxentan was then withdrawn worldwide due to its hepatotoxicity. These data could explain the class-effect mechanism of ETA receptor antagonist drugs and may guide our choice regarding the use of ambrisentan. Currently, ambrisentan is an off-label drug for the treatment of DUs, but it may be considered an alternative to bosentan, at least in cases of adverse effects. However, there is a need for randomised, double-blind, placebo-controlled trials to further evaluate the efficacy of ambrisentan in the prevention and treatment of DUs.

V. TOMASELLI, MD<sup>1</sup>  
D. D'AMBROSIO, MD<sup>1</sup>  
L. MASSARELLI, MD<sup>1</sup>  
D. ROCCATELLO, MD<sup>2</sup>

<sup>1</sup>Department of Medicine, C. Massaia Hospital, Asti, Italy;

<sup>2</sup>Department of Immunology, Haematology, Immunohaematology and Rare Diseases, Centre of Research on Immunopathology and Rare Diseases (CMID), G. Bosco Hospital and University of Turin, Turin, Italy.

Address correspondence to:

Dario Roccatello, Centro Multidisciplinare di Ricerche di Immunopatologia e Documentazione su Malattie Rare (CMID), Ospedale S. G. Bosco, P.zza del Donatore di Sangue 3, 10152 Torino, Italy.  
E-mail: dario.roccatello@unito.it

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