CONNECTIVE TISSUE DISEASES

Treatment of digital ulcers in systemic sclerosis

Sevdalina Lambova and Ulf Müller-Ladner

Digital ulcers in patients with systemic sclerosis (SSc) can cause considerable disability; however, clinical trials addressing the treatment and prevention of digital ulcers in SSc are rare. A study has evaluated the potential benefit of the endothelin receptor antagonist bosentan in the treatment of SSc-related digital ulcers.

Lambova, S. & Müller-Ladner, U. *Nat. Rev. Rheumatol.* **7**, 5–6 (2011); published online 30 November 2010; doi:10.1038/nrrheum.2010.207

Digital ulcers are a frequent and recurrent complication in patients with systemic sclerosis (SSc). Approximately half of these individuals are affected and in 75% of cases the ulcers occur within 5 years of the first observation of non-Raynaud symptoms.[1] An analysis of the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database reveals a high frequency of digital ulcers among the documented 3,656 patients with SSc (1,349 of whom have diffuse SSc, 2,101 have limited SSc and 206 have SSc that overlaps with another connective tissue disease). Overall, 42.7% of the patients with diffuse SSc and about 33% of those with the limited form of the disease suffered from digital ulcers that healed slowly (3–15 months).[2] Digital ulcers frequently persist and are the main cause of pain, impaired hand function and disability in SSc and, in severe cases, hospitalization is required.[1,2]

> “Digital ulcers frequently persist and are the main cause of pain, impaired hand function and disability in SSc...”

The main pathogenic mechanism that contributes to the development of digital ulcers is ischemia owing to SSc-related vasculopathy. Other contributing factors include inflammation, fibrosis of the skin with sclerodactyly, dry skin, calcinosis and secondary infection complicated with osteomyelitis, gangrene, septicemia, autoamputation and/or emergency surgical amputation.[2,3] A study reported that the incidence for finger amputation was 1.2% per patient-year in those with digital ulcers.[1] Immediate therapy should be initiated in these patients to avoid long-term sequelae. As no universal therapeutic approach exists, the current options include vasodilative, analgetic and antiplatelet agents, local antiseptic treatment and antibiotics in case of secondary infection and avoiding exposure to cold temperatures.

Matucci-Cerinic *et al.*[4] have reported the findings from the randomized, double-blind, placebo-controlled study with bosentan on healing and prevention of ischemic digital ulcers in patients with SSc (RAPIDS)-2 trial. Bosentan—a dual endothelin (ET) receptor antagonist—might be of clinical utility as vascular dysfunction is considered to be one of the initial events in SSc. Endothelial injury in SSc results in a decreased production of vasodilators (such as nitric oxide and prostacyclin), which inhibits platelet aggregation and increases the levels of vasoconstrictors such as ET-1, which has proinflammatory and profibrotic properties. ET-1 is also a potent mitogen for fibroblast and smooth muscle cells, a strong stimulant of matrix biosynthesis and is thought to have a major role in the development of structural vascular disorder, organ fibrosis and vascular occlusion in SSc.[5]

Although a variety of pathogenic mechanisms lead to the development of digital ulcers, vasodilators are the main class of drugs used in clinical trials of SSc and are recommended for the management of SSc-related vasculopathy. Calcium-channel blockers, prostanoids and phosphodiesterase-5 inhibitors (such as sildenafil) are effective in Raynaud phenomenon secondary to SSc.[6,7] Digital ulcers, however, remain a serious complication for many patients with SSc. The current EULAR–EUSTAR guidelines for the management of SSc-related vasculopathy recommend dihydropiridine calcium-channel blockers as a first line therapy.

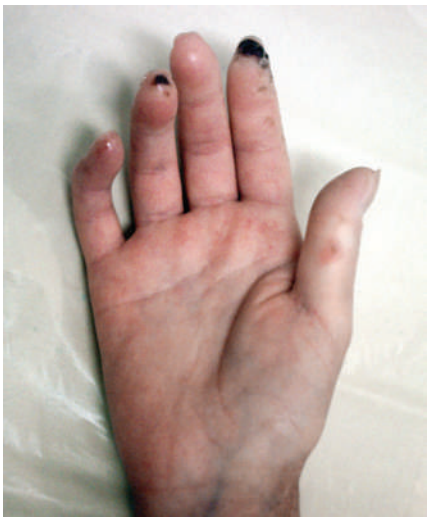

Image courtesy of S. Lambova

The use of these agents has resulted in an improvement in the symptoms of SSc-related Raynaud phenomenon and a resolution of digital ulcers.[6,8] Prostanoids also improve symptoms of digital vasculopathy in SSc and are efficacious for treating digital ulcers, but the intravenous route of administration limits their use in everyday practice.[7,8] In the EULAR guidelines for the treatment of SSc published in 2009,[8] bosentan was recommended for SSc with multiple digital ulcers in patients refractory to calcium channel blockers and prostanoid therapy.

Although the successful treatment of digital ulcers in SSc following treatment with bosentan and other ET receptor antagonists (such as sitaxentan) had previously been reported,[9] high-quality randomized controlled trials addressing the treatment and prevention of digital ulcers were lacking. This scientific gap stimulated the initiation of the RAPIDS-1 trial[10] and, thereafter, the RAPIDS-2 study.[4]

The RAPIDS-1 study randomly assigned 122 patients with a diffuse or limited form

of SSc to receive either bosentan ($n = 79$) or placebo ($n = 43$) with a follow-up period of 16 weeks.[10] Overall, 67.1% of patients in the bosentan group and 55.8% of those in the placebo group suffered from digital ulcers at entry. Bosentan treatment was associated with a 48% reduction in the number of new digital ulcers, particularly in patients with diffuse SSc and multiple digital ulcers. In addition, bosentan treatment resulted in an improvement in hand function.[10]

> “...a considerably reduced number of new digital ulcers was observed in 30% of patients in the bosentan group”

The RAPIDS-2 study, as reported by Matucci-Cerinic *et al.*,[4] involved 41 centers throughout Europe and North America. This large study was designed to evaluate, in detail, the efficacy of bosentan with respect to the healing and prevention of ischemic digital ulcers in SSc. Overall, 188 patients with SSc were randomly assigned to receive either bosentan ($n = 98$) or placebo ($n = 90$). In contrast to the selection criteria for the RAPIDS-1 trial, it was necessary that the patients recruited for the RAPIDS-2 study had experienced at least one prior digital ulcer. In addition, the follow-up period of RAPIDS-2, at 24 weeks, was longer than that of RAPIDS-1. Although inhibition of ET-1 activity did not affect the healing of digital ulcers, a considerably reduced number of new digital ulcers was observed in 30% of patients in the bosentan group, with a more prominent effect in patients with multiple digital ulcers.[4] The main adverse event in the course of treatment with bosentan—as expected from daily clinical practice—was the elevation of transaminases in 14% of patients in the RAPIDS-1 trial and in 12.5% of those in the RAPIDS-2 study. Diarrhea and peripheral edema have also been observed in these patients and serious complications, such as pneumonia and ventricular tachycardia, were reported in single cases.[4,10]

The results from both RAPIDS-1 and RAPIDS-2 demonstrate that patients with SSc develop fewer new digital ulcers following blockade of ET-1 activity with the dual receptor antagonist bosentan, in comparison with placebo. This finding highlights the importance of ET in the pathophysiology of SSc digital ulcers and the role of ET receptor antagonists, specifically bosentan, in the therapeutic algorithm for patients with SSc as outlined in the EULAR–EUSTAR recommendations. The results of RAPIDS-2, however, should also stimulate additional research and clinical studies in this field, which should address not only the healing of digital ulcers, but also the effects of vasodilative combination therapy to improve the overall outcome in the patients with SSc.

*Department for Propedeutics of Internal Medicine, Clinic of Rheumatology, Medical University, Blvd Vasil Aprilov 15A, Plovdiv 4002, Bulgaria (**S. Lambova**). Justus-Liebig University Giessen, Department for Rheumatology and Clinical Immunology, Kerckhoff Clinic, Benekestrasse 2–8, D-61231 Bad Nauheim, Germany (**U. Müller-Ladner**).*
Correspondence to: U. Müller-Ladner
u.mueller-ladner@kerckhoff-klinik.de

Competing interests
S. Lambova declares an association with the European League Against Rheumatism. U. Müller-Ladner declares associations with the following companies: Actelion, GlaxoSmithKline and Pfizer. See the article online for full details of the relationships.

1. Hachulla, E. *et al.* Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. *J. Rheumatol.* **34**, 2423–2430 (2007).
2. Walker, U. A. *et al.* Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. *Ann. Rheum. Dis.* **66**, 754–763 (2007).
3. Galluccio, F. & Matucci-Cerinic, M. Registry evaluation of digital ulcers in systemic sclerosis. *Int. J. Rheumatol.* doi:10.1155/2010/363679.
4. Matucci-Cerinic, M. *et al.* Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomized, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* doi:10.1136/ard.2010.130658.
5. Abraham, D. & Dashwood, M. Endothelin—role in vascular disease. *Rheumatology (Oxford)* **47** (Suppl. 5), v23–v24 (2008).
6. Rademaker, M. *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomized study. *BMJ* **298**, 561–564 (1989).
7. Scorza, R. *et al.* Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. A randomized, controlled study. *Clin. Exp. Rheumatol.* **19**, 503–508 (2001).
8. Kowal-Bielecka, O. *et al.* EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann. Rheum. Dis.* **68**, 620–628 (2009).
9. Humbert, M. & Cabane, J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelia receptor antagonist bosentan. *Rheumatology (Oxford)* **42**, 191–193 (2003).
10. Korn, J. H. *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelia receptor antagonist. *Arthritis Rheum.* **50**, 3985–3993 (2004).

PEDIATRIC RHEUMATOLOGY

JIA, treatment and possible risk of malignancies

Nicolino Ruperto and Alberto Martini

The effect of biological therapies on cancer risk in JIA is controversial owing to confounding factors such as the use of concomitant immunosuppressants. A study has shed new light on this association, but questions still remain on the effect of the disease itself and biological therapies on cancer risk.

Ruperto, N. & Martini, A. *Nat. Rev. Rheumatol.* **7**, 6–7 (2011); published online 7 December 2010; doi:10.1038/nrrheum.2010.199

The use of tumor necrosis factor (TNF) inhibitors has represented a major advance in the treatment of juvenile idiopathic arthritis (JIA).[1] In 2008, the FDA issued an early communication (black box warning)[2] about a possible association between the use of TNF blockers and the development of lymphoma and other cancers in children and young adults with JIA, Crohn's disease or other diseases treated with anti-TNF agents.

In 2010, Diak *et al.*[3] reported the results of their search of the FDA Adverse Events Reporting System (AERS) to identify malignancies associated with the use of anti-TNF agents in children, such as infliximab, etanercept and adalimumab (although information related to adalimumab is limited as it is the latest anti-TNF agent to come to market). The reporting rate for all malignancies were 66 and 22 malignancies per 100,000 patients