Case Report

Efficacy of Bosentan in Treatment of Unresponsive Cutaneous Ulceration in Disabling Pansclerotic Morphea in Children

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ABSTRACT. Disabling pansclerotic morphea (PM) of childhood is a rare and debilitating variant of localized scleroderma. We describe a 4-year-old girl with rapid progression of deep cutaneous fibrosis extending into the muscle fascia with disabling joint contractures of the hips, knees, ankles, and fingers and recalcitrant ischemic ulcerations. Within the first months of therapy with dual oral endothelin receptor antagonist bosentan (31.25 mg qid for 4 weeks, then 31.25 mg bid) limb ulcers improved, with resolution of the widespread sclerotic skin lesions. Joint mobility improved, and a substantial decrease of skin thickness was noted. No side effects were noted. In the context of other data in scleroderma, bosentan may be a promising option in the treatment of PM. (J Rheumatol 2006;33:2538–40)

Key Indexing Terms:
BOSENTAN PANSCLEROTIC MORPHEA LOCALIZED SCLERODERMA EFFICACY

Disabling pansclerotic morphea (PM) of childhood is a rare and severe variant of localized scleroderma. It is characterized by rapid progression of deep cutaneous fibrosis, severe joint contractures and cutaneous ulcerations. It typically appears in childhood and is associated with impaired quality of life and poor prognosis[1]. Spontaneous regression in PM is rare, and there is no current effective therapy for this condition[2]. Overexpression of endothelin is seen in skin, in ischemic ulcerations in systemic sclerosis (SSc), and in pulmonary arterial hypertension (PAH) that may, among other manifestations, occur in association with SSc[3].

Bosentan is an orally active dual endothelin (ET_A/ET_B) receptor antagonist effective in the treatment of PAH, including PAH associated with SSc[4]. In several case reports and 2 recent randomized controlled studies (Rapids-1 and Rapids-2) it also had a beneficial effect on other manifestations of SSc such as ischemic digital ulcerations and cutaneous fibrosis[5-9].

CASE REPORT

A 4-year-old girl with a history of celiac disease was first seen in our hospital in 2001 with a 4-month history of rapidly progressive morphea. There was no significant family history of connective disease, medication intake, or toxin exposure. Skin involvement consisted of both deep and superficial cutaneous sclerosis. The condition worsened with development of deep subcutaneous fascia, tendon, and ligament involvement. The solid sclerotic and later atrophic changes produced a loss of musculoskeletal function, with disabling joint contractures of the hips, knees, ankles, and fingers. Subsequently, she developed cicatricial plaques localized on the dorsum of the hands and feet accompanied by pigmentary changes. Later, some of these areas became progressively ulcerated and severe ankylosis of the ankles and knees developed. There was no history of Raynaud's phenomenon, dysphagia, or dyspnea. Investigations showed an elevated serum IgG of 1940 mg/dl (normal 800–1800 mg/dl), antinuclear antibody-positive titer of 1:80, anti-endomysial antibodies 1:320 (positive > 1/5), anti-gliadin G 125 mg/dl (positive > 30 mg/dl), anti-gliadin A 9 mg/dl (positive > 3 mg/dl), and peripheral blood eosinophilia (30%) with high leukocyte count of 13,000/mm^3. The test for Scl-70 was negative. Chest radiograph was normal. Pulmonary function tests showed decreased diffusion of carbon monoxide and decreased vital capacity, with normal residual volume due to chest wall restriction. An echocardiogram was normal. Histopathological evaluation of the skin biopsy showed a lymphocytic and hyaline panniculitis.

The child was sequentially treated with corticosteroids, D-penicillamine, methotrexate, calcium channel blockers, angiotensin-converting enzyme inhibitors, and topical antiseptic therapy, without clinical response. Corticosteroids, D-penicillamine, and methotrexate were withdrawn because of lack of response and the appearance of significant liver toxicity. Next, she received biweekly psoralen plus ultraviolet A (PUVA) therapy for a 6-month period. PUVA therapy was well tolerated and no side effects were observed. During the first month there was skin softening on the trunk, but over a 12-month period the plaques expanded to confluence and multiple foot ulcerations appeared (Figure 1). Contractures and ankylosis of the hands and feet worsened, and general mobility was impaired.

Bosentan was started on a compassionate-use basis in February 2005 with informed consent from a parent. The initial dose was 31.25 mg qid for 4 weeks, and then adapted to the standard dose for her weight (16 kg), 31.25 mg bid. Within the first months of bosentan therapy, limb ulcers improved, with resolution of the widespread sclerotic skin lesions (Figure 2); joint mobility improved with physiotherapy, with an increase of mobility of 10° in every involved joint, and a substantial decrease of skin thickness. Safety was evaluated by monitoring adverse events and liver function by monthly assessment

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Accepted for publication July 31, 2006.

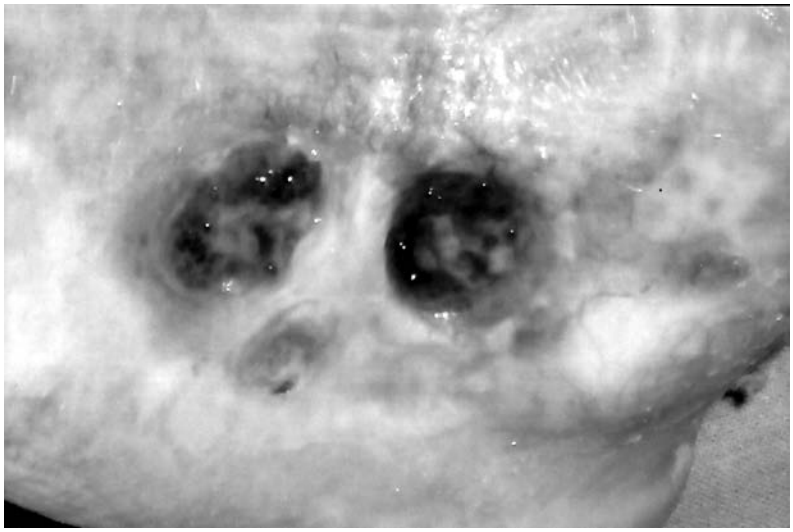

Figure 1. Active ulcer in the ankle area before bosentan therapy.

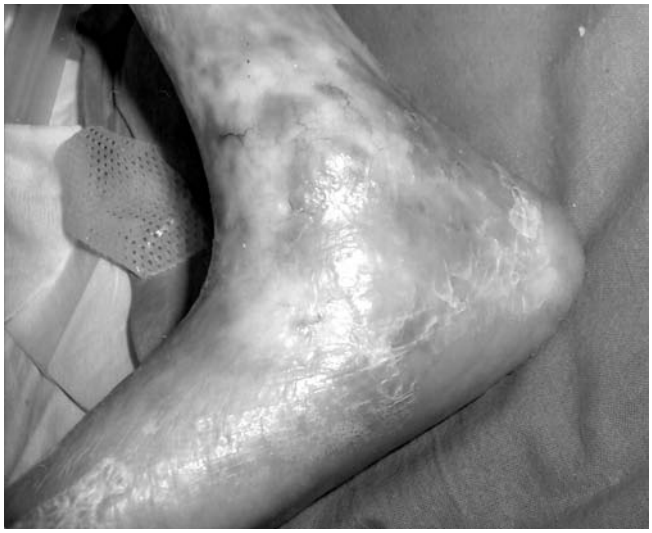

Figure 2. Improvement in the same ulcer after 7 months of bosentan therapy. The ulcer resolved completely.

of hepatic transaminase levels. No side effects were observed. The elevated antinuclear antibody titers remained unchanged. There was no systemic disease involvement. The girl's condition is now stable and she is able to take part in normal school and leisure activities (per Childhood Health Assessment Questionnaire).

DISCUSSION

Since the first description of pansclerotic morphea, few cases have been reported[1,10-12]. To date, there is no satisfactory treatment. Most recent cases have been empirically treated with UVA or PUVA therapy[13-15]. In our patient, we observed an improvement in the skin on the trunk, but the disease was complicated by the development of chronic, progressive ischemic foot ulcerations. Continuous or longterm treatment with vasodilators and antibiotics may be required to prevent secondary infections and prevent the need for amputation. The prostaglandin analogs have potent vasodilator and antiplatelet effects, although intravenous administration is a drawback.

The BREATHE-3 study provides valuable data regarding the tolerability and safety for bosentan, an orally active, dual endothelin receptor antagonist, in pediatric patients with PAH[16]. Endothelin-1 (ET-1) is a potent endogenous vasoconstrictor and a mitogen for fibroblasts, smooth muscle, and endothelial cells. It is released by scleroderma fibroblasts *in vitro* and may increase dermal fibrosis in SSc. In addition, ET-1 levels are increased in patients with SSc, and evidence suggests that it plays a significant role in the pathogenesis of other collagen vascular diseases[3].

These results support a multiple role for ET-1 in the pathophysiology of scleroderma associated with PAH and skin ulcerations. The rapid response to bosentan treatment in our patient's skin ulcers, and the improvement in her cutaneous fibrosis, could be a result of dual endothelin receptor antagonism blocking the opposing vasoconstrictive and profibrotic effects of endothelin. Our case suggests a role for bosentan to treat the vasculopathy of disabling pansclerotic morphea in children.

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