Acta Derm Venereol 2011; 91: 686–688

CLINICAL REPORT

Abatacept is a Promising Treatment for Patients with Disseminated Morphea Profunda: Presentation of Two Cases

Birgitte STAUSBØL-GRØN[1], Anne B. OLESEN[1], Bent DELEURAN[2] and Mette S. DELEURAN[1]
Departments of [1]Dermato-Venereology and [2]Rheumatology, Århus University Hospital, Århus, Denmark

Morphea profunda is a rare disease that mainly affects young women and often has a progressive course with physical and psychological sequelae. The skin becomes sclerotic after an initial inflammatory reaction and joint contractures can develop. The aetiology is unknown. Until now, no successful therapy has been proven for this morphea variant. On the basis of new insights into the key role of effector T cells in scleroderma, in particular Th-17, T-cell directed therapies are expected to have promising effects. We report here the first two cases of morphea profunda treated with abatacept. Abatacept had a clinical effect on the active disease, in addition to softening old sclerotic lesions. ***Key words: abatacept; morphea profunda; mRodnan skin score; Orencia.***

(Accepted February 13, 2011.)

Acta Derm Venereol 2011; 91: 686–688.

Birgitte Stausbøl-Grøn, Department of Dermato-Venereology, Århus University Hospital, P.P. Ørumsgade 11, DK-8000 Århus C, Denmark. E-mail: birgstau@rm.dk

In scleroderma, the skin becomes sclerotic after an initial inflammatory reaction. The dermis in particular becomes thickened and hardened. The localized form, morphea, may cause physical and psychological sequelae, in particular the disabling pansclerotic morphea and morphea profunda (1). These variants of the disease may feature sclerosis in the connective tissue septa of the subcutaneous fat and in the underlying muscle fascia. The skin becomes bound to the deeper structures and typically develops a depressed or bumpy surface. In severe cases joint contractures can develop.

Morphea is an uncommon disorder. It is more frequent among women, and in young adults aged 20–40 years. The aetiology of morphea is unknown. It is believed that inflammatory processes in the skin induce increased synthesis of collagen from fibroblasts. A possible implication of the effector $CD4^+$ T-cell subpopulation Th-17 has been suggested in the pathogenesis of scleroderma (2).

At present, active superficial morphea can be treated with ultraviolet A1 (UVA1) with good results (3). Meanwhile, there is no efficient therapy for the profound, progressive and destructive morphea variants (1, 4). On the basis of new insights into the key role of effector T cells, in particular Th-17, T-cell directed therapy including abatacept has been proposed to be clinically beneficial (4). We describe here two patients treated with abatacept (Orencia) for chronic and progressive disseminated morphea profunda. Abatacept is a recombinant fusion protein that selectively inhibits T-cell activation via competitive binding to CD80 or CD86, where T cells are involved in the disease pathophysiology (5). It is approved for the treatment of rheumatoid arthritis.

CASE REPORTS

Case 1

The first patient, an otherwise healthy 47-year-old woman, had first presented with clinical morphea lesions when she was 22 years old. A punch biopsy showed typical histological findings of morphea. The patient had no other organ-specific manifestations. Routine blood evaluation was normal. Antinuclear antibody (ANA) was positive. SSA, SSB, Scl-70, ENA, anti-cardiolipin and RNA-polymerase were all negative.

Previously, because of exacerbations in the disease, the patient had been treated with penicillamine, prednisolone, cyclosporine, high-potency corticosteroid ointment under occlusion, methotrexate, UVA1 (50 treatments), antimalarials and mycophenolate mofetil, in addition to physiotherapy. None of these treatments had any convincing effect on controlling disease activity.

In May 2009, the patient had a further exacerbation of the disease, with new lesions and severe pruritus. Clinically, she had disseminated morphea, mainly on the extremities, involving the skin over the joints. Some lesions were new and active yellow-white lesions with a lilac ring; others were older and more sclerotic and atrophic with hyperkeratotic changes. Extensive post-inflammatory hyperpigmentation was also seen (Fig. 1).

A punch biopsy from an active lesion on the left thigh confirmed the diagnosis and showed a primarily lymphocytic inflammatory infiltrate around the superficial and deep blood vessels. Furthermore, inflammation at the junction between the dermis and the subcutaneous fat was observed, and the dermal collagen fibres were thickened.

Before treatment with abatacept, screening tests for hepatitis and tuberculosis were negative. X-ray of the thorax was normal.

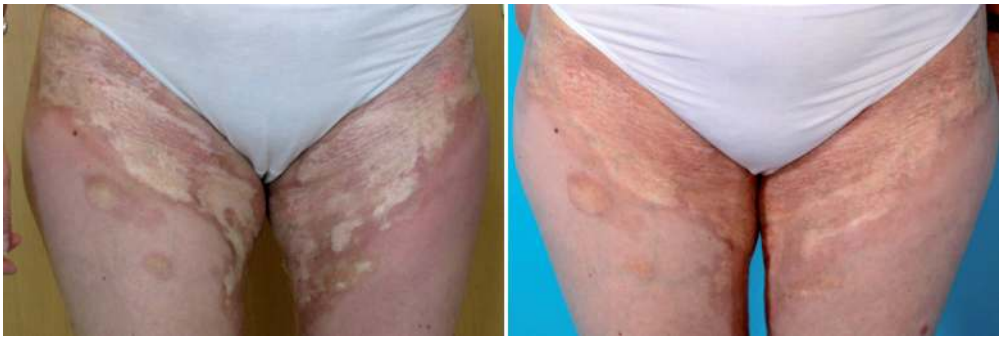

Fig. 1. Patient No. 1 with disseminated morphea profunda (a) before treatment with abatacept and (b) after 16 treatments.

Following oral and written informed consent, the patient was treated with 750 mg abatacept intravenously on days 1, 15, and 30, and thereafter every 4–6 weeks, according to her weight (66 kg). She has thus far received 20 treatments.

During the treatment period, she developed hypertension, which is a known side-effect of abatacept. At the same time, she was treated with 15 mg prednisolone, which was carefully tapered to 0 before the 11th treatment with abatacept. After treating the hypertension with calcium antagonists and diuretics, her blood pressure was stable. Furthermore, control blood tests were normal during treatment.

The treatment with abatacept was well tolerated. The patient felt less itchy, and the joint motion was increased. The disease activity was reduced, both when evaluating the whole body and the single lesions. The erythema around the lesions decreased (Fig. 1), and the older lesions became softer. The effect of the treatment was scored by modified Rodnan skin score (6). This total skin thickness score is commonly used as an outcome measure in trials of systemic sclerosis. Skin thickness is assessed by clinical palpation of 17 body areas on the front side on a 0–3 scale (normal, mild, moderate and severe). The modified Rodnan skin score is derived by summation of the scores from all 17 body areas. Previously, assessment of the skin score has been sufficiently reproducible to be included as a measure of treatment outcome (6). Our first patient had a modified Rodnan skin score of 18 before treatment start, and a score of 2 after 20 treatments. The evaluations were performed by BSG and ABO, separately or together (Table I).

Since the clinical response has been good and the patient has had no severe adverse events, the treatment is continuing. We have increased the time intervals between treatments to 6 weeks, and we continue to monitor the effect on the skin and joints.

Case 2

The second patient, a 38-year-old woman developed diffuse progressive morphea profunda, when she was 8 years old. The skin on her shoulders, back and right lower leg has been mainly affected. As a result, the right leg is rotated outwards and the flexion of the right knee and foot is reduced. No other organ-specific involvements have been observed. All blood samples have been normal. Previously, because of disease activity, the patient has been treated with penicillamine, prednisolone, cyclosporine and UVA1 (31 treatments).

Because of exacerbation of the morphea profunda with progression of inflammation and fibrosis in the old lesions, after giving birth to her third child, the patient was treated with 7.5 mg prednisolone daily together with abatacept. The patient had symmetrical severe deep fibrotic lesions on her shoulders, upper arms, buttock and right thigh, with a modified Rodnan skin score of 13. The deep fibrotic lesions were atrophic and hyperpigmented, with a typical lilac ring in the periphery of the lesions (Fig. 2).

Before treatment with abatacept, a screening test for tuberculosis was positive. As a child, she had undergone Calmette vaccination against tuberculosis. For safety, she was treated for 4 weeks with prophylactic rifampicin and isoniazid.

The treatment, abatacept 500 mg, was given intravenously on days 1, 15, and 30 and thereafter every 4 weeks according to her weight (58 kg). The patient received a total of five treatments. She experienced an impressive improvement, and reported better movement of the shoulders, hips and knees. She could walk longer distances and had no adverse effects. In addition, it was possible to stop the prednisolone treatment after 4 treatments of abatacept. On evaluation after 12 weeks the inflammatory lesions had disappeared. After 7 months, the modified Rodnan skin score was 6 (Fig. 2).

Unfortunately, abatacept treatment had to be stopped after 2.5 months, as the patient was diagnosed with

Table I. *Modified Rodnan (mRodnan) skin score before and during treatment with abatacept in patient no. 1*

Abatacept treatments, *n*	Time, months	mRodnan skin score
0		18
4	2	15.5
7	5	8.5
9	7	9
13	10	9.5
15	12	7.5
20	19	2

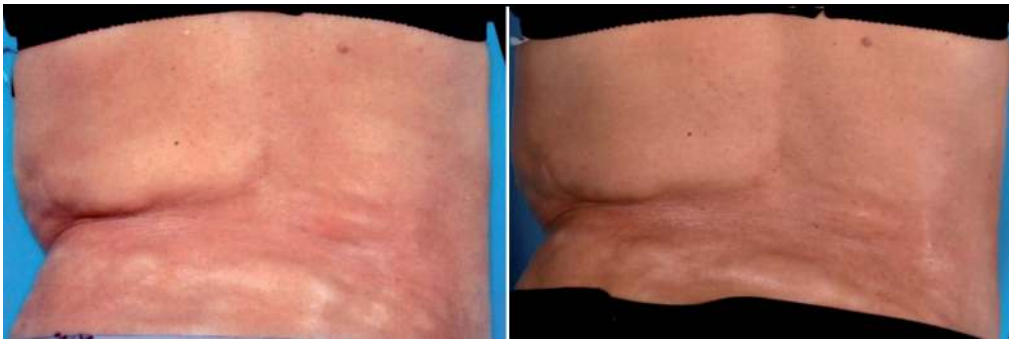

Fig. 2. Patient No. 2 with disseminated morphea profunda (a) before treatment with abatacept and (b) after 5 treatments.

breast cancer. We do not think that this disease is related to the treatment with abatacept, but it has been reported to the Danish Medicines Agency.

DISCUSSION

This case report describes the first two patients with disseminated morphea profunda treated with abatacept. Morphea profunda is a rare disease and often runs a progressive course with physical and psychological sequelae. Until now, no treatment has been proven effective on active disease or been able to soften old sclerotic lesions (1).

Our first patient is very satisfied with the abatacept treatment. She feels less itchy, has better joint movements and the treatment is well tolerated. The modified Rodnan skin score has reduced significantly during treatment. Thus, the disease activity has been diminished both when evaluating the whole body and the erythema around the single lesions. Even the older lesions feel softer on examination. Furthermore, it has been possible to taper the prednisolone treatment.

Our second patient was also satisfied, as abatacept improved her joint movements and walking distance. This patient was also able to stop prednisolone treatment. However, this patient had to stop after 5 treatments with abatacept. After the treatment was stopped, a further softening effect on the old lesions was observed.

Thus, we report here the first cases of diffuse morphea profunda, treated successfully with abatacept, which is an inhibitor of T-cell activation. The mechanism is unknown, but the expansion of T cells in the affected skin and circulation from patients with systemic sclerosis suggests antigen-specific activation. Th-17 and regulatory T cells, which are subsets of effector T cells, are key regulators of inflammation in several autoimmune diseases (2, 7).

Abatacept was well tolerated. However, the long-term effect of abatacept needs to be established. In addition, a randomized, double-blinded placebo-controlled clinical trial of abatacept for diffuse morphea profunda is necessary. A trial investigating the effect of abatacept for diffuse systemic scleroderma is currently in progress (8). This report gives examples of the clinical effect of abatacept in morphea profunda.

The authors declare no conflict of interest.

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