LETTERS

Targeting activated T cells: successful use of anti-CD25 monoclonal antibody basiliximab in a patient with systemic sclerosis

H U Scherer, G-R Burmester, G Riemekasten

Ann Rheum Dis 2006;**65**:1245–1247. doi: 10.1136/ard.2005.046938

Serum levels of soluble interleukin (IL) 2 receptor strongly correlate with skin involvement, disease progression and mortality in systemic sclerosis (SSc).^{1,2} This finding underlines the role of activated and possibly dysregulated T cells in the pathogenesis of the disease. Specifically targeting these cells may therefore be a new therapeutic approach. Basiliximab is a chimeric monoclonal antibody directed against the α chain (CD25) of the IL2 receptor.³ It is approved for the treatment of kidney allograft rejections. Here, we describe the successful use of basiliximab

in combination with cyclophosphamide in a patient with severe, rapidly progressive SSc.

In February 2004, a 43-year-old woman with a 3-year history of Scl-70-positive, diffuse SSc presented to our department. Despite prior treatment with methotrexate, prostacycline infusions, azathioprine and calcium channel blockers, the patient presented with severe Raynaud's phenomenon, digital ulcers (fig 1A) and progressive skin thickening. Polymorphic ventricular premature complexes, tricuspid regurgitation of IV° (no coaptation of flaps),

Before treatment
(February 2004)

Month 6
(August 2004)

Month 9
(November 2004)

Basiliximab
 Intravenous pulse cyclophosphamide
 Prednisolone (7.5 mg > 10 mg/day)
 Intravenous prostacycline (5–10 days per month)

Figure 1 Regression of skin ulcers during therapy with basiliximab (A) before start of treatment, (B) after 6 months of treatment and (C) further improvement and prolonged effect after the end of basiliximab treatment. Mod., modified.

Table 1 Selected laboratory and diagnostic findings and their change over time during treatment with basiliximab

	February (before treatment)	May (month 3)	August (month 6)	Reference
sIL2-R (Immulite assay in IU/ml)	926.0	556.0	659.0	<1000
Leucocytes (/nl)	14.02	11.52	8.63	4.5–11.0
CRP (mg/dl)	4.2	1.02	2.46	<0.5
Creatine kinase (U/ml)	206	39	40	<145
CK-MB (U/ml)	33	n.d.	n.d.	<24
Myoglobin (μ g/l)	112	n.d.	n.d.	<70
Creatinine (mg/dl)	1.36	0.85	0.70	<1.0
Proteinuria (mg/d)	306	Negative	Negative	$\leq$ 150
Creatinine clearance (ml/min)	58	n.d.	106	90–130
Pericardial effusion (echocardiography in mm)	15–30	n.d.	5–11	
PAP (systole/diastole//mean in mm Hg)	26/17//18	n.d.	26–30 (calculated)	6–30/4–13//9–18
PCWP (systole/diastole//mean in mm Hg)	6/5//4	n.d.	n.d.	4–12
Cardiac index (l/min/m ²)	1.6	n.d.	n.d.	2.5–4.0
FVC (l)	1.79 (53.7)	1.73 (52.1)	1.43 (43.3)	% of predicted given in ()
FEV ₁ (l)	1.52 (52.9)	1.46 (51.1)	1.18 (41.3)	% of predicted given in ()
TLC (l)	3.64 (69.6)	3.57 (68.2)	2.87 (54.9)	% of predicted given in ()
DLCOC SB (mmol/min/kPa)	3.47 (39.8)	n.d.	2.91 (47.5)	% of predicted given in ()

CK-MB, creatine kinase-myoglobin; CRP, C reactive protein; DLCOC SB, corrected carbon monoxide diffusion capacity using the single breath method; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; ; TLC, total lung capacity.

dyspnoea at rest and pericardial effusion (30 mm) suggested cardiac involvement. Pulmonary artery pressure as assessed by right-heart catheterisation was normal. A high-resolution computed tomography scan showed mild basal “ground-glass” opacification indicative of interstitial lung disease (<10%). Table 1 summarises additional findings.

Faced by rapid disease progression with predominant cardiac and skin involvement despite conventional treatment, we started treatment with intravenous pulse cyclophosphamide (CYC, 1 g/month), prednisolone (initial dose 75 mg/day, reduced to 10 mg/day in June), angiotensin-converting enzyme inhibitor, prostacycline infusions (5–10 days a month) and, with a delay of 3 weeks, basiliximab as additional selective immunosuppressant. Alternative options such as oral CYC or high-dose glucocorticoids were discussed but deemed hazardous as they implied the risk of renal crisis or serious infections. Basiliximab (20 mg) was given twice in weekly intervals, followed by an infusion at day 28 and at monthly intervals thereafter. In total, basiliximab was given for 6 months. Thereafter, only CYC, prostacycline and low-dose prednisolone were continued.

Therapeutic efficacy was most prominent with regard to skin involvement (fig 1B). Modified Rodnan Skin Score reduced from 24 to 19 in 6 months, with a further reduction to 11 at month 9 (fig 1C). Cardiac involvement also reduced (table 1), but the structural damage remained. Lung involvement showed improvement in corrected carbon monoxide diffusion capacity, but forced vital capacity worsened.

Activated T cells have been associated with skin involvement and disease activity in SSc.^{1–2} Soluble IL2 receptor, large numbers of CD69 or CD3 infiltrating T cells and oligoclonal expansion of T cells suggesting antigen-specific activation have been found in scleroderma skin lesions.^{4–6} T cells are thought to be activated early during disease development, leading to fibroblast activation through cytokine secretion and cell-to-cell contact. Considering these observations, rapid disease progression and short overall disease duration in our patient, we decided to intensify treatment by selectively targeting activated T cells with anti-CD25 monoclonal antibody basiliximab. It is impossible to attribute aspects of efficacy solely to basiliximab in this setting of combination treatment. Excellent, rapid and sustained improvement in skin involvement, however, exceeded our expectations, which were based on published data.

Combination regimen comprising intravenous pulse CYC and prednisolone have mostly been evaluated with regard to

SSc-related interstitial lung disease.^{7–9} Albeit methodological differences, small but consistent improvements in pulmonary function tests have been reported by various authors, generally in 6 months of treatment.⁹ Improvement of skin involvement has rarely been assessed, including one study reporting a mean reduction in modified Rodnan Skin Score of 4.9 after 6 months and 5.4 after 12 months.⁷ More prominent effects have been described in patients with early SSc treated with oral CYC.¹⁰

The case presented points towards a beneficial effect of targeting activated T cells in skin involvement in SSc, especially early in the course of disease.

ACKNOWLEDGEMENTS

GR acknowledges financial support from the German Network for Systemic Sclerosis (Bundesministerium für Bildung und Forschung (BMBF)) and from the EUSTAR (EULAR) programme.

Authors' affiliations

H U Scherer, G-R Burmester, G Riemekasten, Department of Rheumatology and Clinical Immunology, Charité—University Medicine Berlin, Berlin, Germany

Competing interests: None declared.

Correspondence to: H U Scherer, Department of Rheumatology and Clinical Immunology, Charité—University Medicine Berlin, Schumannstrasse 20-21, 10117 Berlin, Germany; ulrich.scherer@charite.de

Accepted 3 April 2006

REFERENCES

- 1 Degiannis D, Seibold JR, Czarnecki M, Raskova J, Raska K Jr. Soluble interleukin-2 receptors in patients with systemic sclerosis. Clinical and laboratory correlations. *Arthritis Rheum* 1990;**33**:375–80.
- 2 McHugh NJ, Distler O, Giacomelli R, Riemekasten G. Non organ based laboratory markers in systemic sclerosis. *Clin Exp Rheumatol* 2003;**21**(Suppl 29):S32–8.
- 3 Church AC. Clinical advances in therapies targeting the interleukin-2 receptor. *QJM* 2003;**96**:91–102.
- 4 Sondergaard K, Stengaard-Pedersen K, Zachariae H, Heickendorff L, Deleuran M, Deleuran B. Soluble intercellular adhesion molecule-1 (sICAM-1) and soluble interleukin-2 receptors (sIL-2R) in scleroderma skin. *Br J Rheumatol* 1998;**37**:304–10.
- 5 Kalogerou A, Gelou E, Mountantonakis S, Settas L, Zafiriou E, Sakkas L. Early T cell activation in the skin from patients with systemic sclerosis. *Ann Rheum Dis* 2005;**64**:1233–5.
- 6 Sakkas LI, Xu B, Artlett CM, Lu S, Jimenez SA, Platsoucas CD. Oligoclonal T cell expansion in the skin of patients with systemic sclerosis. *J Immunol* 2002;**168**:3649–59.

- 7 Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. *J Rheumatol* 2002;29:298–304.
- 8 Giacomelli R, Valentini G, Salsano F, Cipriani P, Sambo P, Conforti ML, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. *J Rheumatol* 2002;29:731–6.
- 9 Airo P, Danieli E, Parrinello G, Antoniali CM, Cavazzana I, Toniati P, et al. Intravenous cyclophosphamide therapy for systemic sclerosis. A single-center experience and review of the literature with pooled analysis of lung function test results. *Clin Exp Rheumatol* 2004;22:573–8.
- 10 Calguneri M, Apras S, Ozbalkan Z, Ertenli I, Kiraz S, Ozturk MA, et al. The efficacy of oral cyclophosphamide plus prednisolone in early diffuse systemic sclerosis. *Clin Rheumatol* 2003;22:289–94.

Resolution of sclerodermatous myocarditis after autologous stem cell transplantation

M Al-mashaleh, H Bak, J Moore, N Manolios, H Englert

Ann Rheum Dis 2006;65:1247–1248. doi: 10.1136/ard.2005.048405

Cardiac involvement in scleroderma is often subclinical^{1–3} and occurs early in the disease.^{4–5} The myocardium, pericardium and conduction system may be affected, resulting in heart failure or arrhythmia.⁶ Symptomatic pericarditis occurs in 7–20% of patients, whereas histological involvement has been reported to be as high as 70–80% at autopsy.⁶

We believe this is the first report of a man with symptomatic sclerodermatous myocarditis in whom the myocarditis resolved after initial pulse cyclophosphamide treatment followed by autologous stem cell transplantation (ASCT).

A 37-year-old mining electrician developed Raynaud's syndrome, skin thickening and polyarthritis in September 2003. Scleroderma was diagnosed 4 months later. By July 2004, he noted a 22 kg weight loss, night sweats, heartburn, nausea, muscle weakness and exertional dyspnoea. Clinical examination showed marked cachexia, widespread scleroderma (except the back), persistent tachycardia, a fourth heart sound, widespread tendon friction rubs, proximal muscle weakness and tender joints. Respiratory examination was normal. Abnormal investigations included high erythrocyte sedimentation rate (71 mm at the end of the first hour), C reactive protein (41 mg/l; normal <5), creatine kinase (1368 U/l; normal <186), troponin (0.74 ng/ml; normal <0.03), lactate dehydrogenase (454 U/l; normal <225), aspartate transaminase (62 U/l or 109 g/l), antinuclear antibodies (1:640 speckled) and extractable nuclear antigen Scl-70 positive. Renal function was normal. An electrocardiogram showed bifascicular block and low voltage in the frontal leads, with reduced ejection fraction (45%), mild mitral and tricuspid regurgitation and a mildly dilated right ventricle. Myocarditis, myositis, tenosynovitis and synovitis were diagnosed.

Initial treatment comprised methylprednisolone and cyclophosphamide (intravenous, 6 times), cyclosporin (50 mg daily) and captopril (6.25 mg twice daily). The patient remained normotensive.

The synovitis, myositis and cardiomegaly resolved, and his weight stabilised. The myocarditis improved (creatinine kinase, 180 U/l; troponin, 0.14 ng/ml), but the scleroderma worsened (affecting the upper back). The tenosynovitis remained problematic.

He underwent non-manipulated ASCT with high-dose cyclophosphamide (50 mg/kg for four doses) and equine-ATG (500 mg) in January 2005.

By day 5 after transplant, the troponin (0.05 ng/dl) and creatine kinase (84 U/l) had normalised. An echocardiogram (day 14) showed an improved ejection fraction (60–65%), normal left ventricle, slightly increased right ventricle and right atrium; electrocardiogram findings remained unchanged.

The patient's weight loss has resolved since then, the modified Rodnan Skin Score has fallen to 15 (from 28) and levels of cardiac enzymes have remained normal.

The coexistence of cardiomegaly, increased levels of cardiac enzymes, tachycardia, reduced ejection fraction, abnormalities on electrocardiogram, presence of inflammatory features in other organ systems and resolution after intense immune suppression, in the absence of other causes, was consistent with features of scleroderma myocarditis. The persistent conduction abnormality after ASCT was attributed to conduction pathway fibrosis.

Suggested eligibility criteria for ASCT in scleroderma include recent onset, presence of association of vital organs (lung, heart or kidneys) and, in one ongoing trial, absence of prior occupational silica exposure.⁷

Previous studies have noted the objective clinical changes after ASCT in improving skin scores and stabilising involvement of vital organs.^{8–9} In this patient, skin tightness and myocardial function not only stabilised but also improved despite the presumed persistence of endogenous silica. Some studies showed that early immunosuppressive treatment with high-dose corticosteroids and pulse intravenous cyclophosphamide results in good cardiac outcome in acute lupus myocarditis.¹⁰

This case report highlights the therapeutic benefit of ASCT in the treatment of sclerodermatous myocarditis, and in scleroderma affecting skin, tendon sheaths and skin in a patient with early diffuse scleroderma positive for exposure to silica.

Authors' affiliations

M Al-mashaleh, H Bak, N Manolios, H Englert, Rheumatology Department, Westmead Hospital, Sydney, Australia
J Moore, Haematology Department, St Vincent's Hospital, Sydney

Competing interests: None declared.

Informed consent was obtained from the patient for publication of his details in this report.

Correspondence to: H Englert, Rheumatology Department, Westmead Hospital, PO Box 533, Wentworthville, Sydney, NSW 2165, Australia; manal_mashaleh@yahoo.com

Accepted 18 February 2006

REFERENCES

- 1 Liangos O, Neure L, Kuhl U, Pauschinger M, Sieper J, Distler A, et al. The possible role of myocardial biopsy in systemic sclerosis. *Rheumatology* 2000;39:674–9.
- 2 Saccardi R, Tyndall A, Coghlan G, Denton C, Edan G. Consensus statement concerning cardio toxicity occurring during haematopoietic stem cell