Hematopoietic stem cell transplantation for systemic sclerosis: history and current status

Richard K. Burt[a] and Francesca Milanetti[b]

[a]Division of Immunotherapy, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA and [b]Division of Clinical Immunology and Rheumatology, Sant'Andrea Hospital, 'Sapienza' University of Rome, Italy

Correspondence to Richard K. Burt, MD, Division of Immunotherapy, Northwestern University Feinberg School of Medicine, Rubloff Bldg, Room 647, Chicago Ill, 60611, USA
E-mail: rburt@northwestern.edu

Current Opinion in Rheumatology 2011, 23:519–529

Purpose of review

Systemic sclerosis (SSc) remains one of the last severe autoimmune disease with a poor prognosis and modest response to immunosuppressive therapy. Mortality in severe diffuse disease with internal organ involvement is elevated. Autologous hematopoietic transplantation (HSCT) has emerged in the last decade as a promising disease-modifying treatment.

Recent findings

In phase I/II trials, HSCT has demonstrated to induce impressive reversal of skin fibrosis, neoangiogenesis, improved functionality and quality of life, and stabilization of internal organ function. Treatment-related mortality was reduced over time by better pretransplant evaluation and by treating patients earlier in disease.

Summary

Two out of three randomized trials of autologous HSCT for SSc have been concluded: the nonmyeloablative American Systemic Sclerosis Immune Suppression versus Transplant, and Autologous Stem cell Transplantation International Scleroderma. The myeloablative Scleroderma Cyclophosphamide versus Transplant instead is still recruiting patients. The soon expected results from these trials should clarify the role of autologous HSCT in the challenging management of severe SSc.

Keywords

hematopoietic stem cell, scleroderma, systemic sclerosis, transplantation

Curr Opin Rheumatol 23:519–529

1040-8711

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease of unknown etiology characterized by fibrosis of the skin and internal organs. Its clinical manifestations are heterogeneous and reflect three major pathogenic events: endothelial dysfunction, fibroblast dysfunction, and dysregulation of the immune system. SSc is divided into two subgroups, limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [1]. Some believe that these two groups are two separate forms of the disease, particularly given differences in outcome, serology, and genetics.

Survival

The prognosis for limited SSc is significantly better than diffuse with a mortality of 1–4% versus 5–10% per year, respectively [2]. Several studies have evaluated extent of skin and organ involvement, nail bed capillary involvement, autoantibodies, and signs of inflammation or immune activation for prognostic significance. In univariate analysis, numerous poor prognostic factors have been reported including diffuse skin involvement [3–13], male sex [3,8,10,14], older age at the onset of the SSc [3–7,9,13,15–17], internal organ involvement including the heart [3–9,12,14–16,18–20], kidney [3,4,6–8,13,16–18,20,21], gastrointestinal tract [6,18,21], lung [3–9,14,17,18,21,22], presence of pericardial effusion or pericarditis [7,8,17], clinical signs of right heart failure [9,14], antitopoisomerase antibody positivity [4,5,9], anemia [5–7,16,17,21], increased erythrocyte sedimentation rate (ESR) [4–7,13,16,22], increased C reactive protein [8], abnormal urine sediment [5,19], proteinuria [5,16], pigmentation disturbances [6,13], and elevated peripheral blood soluble tumor necrosis factor alpha-receptor, or soluble interleukin-2 receptor [23]. Conversely, anticentromere antibody positivity [24,25], limited skin involvement [25], or improvement in skin thickening (decrease in modified Rodnan skin score by 25% or more) conveys a favourable prognosis [26,27].

A few studies have attempted multivariate analysis to identify independent predictors of mortality (Table 1) [3–5,7–9,13–15,17,19,22,28,29,30••,31,32]. Independent predictors for survival from the multivariate analysis are shown in Table 1 and include male sex, diagnosis of neoplasm, pulmonary involvement [lung carbon monoxide diffusing capacity (DLCO) or forced vital capacity (FVC) <70%], renal involvement (proteinuria, elevated

creatinine, low creatinine clearance, diastolic hypertension, prior renal crisis, or elevated blood urea nitrogen), cardiac involvement (arrhythmia, heart failure, persistent moderate-to-large pericardial effusion, pulmonary artery hypertension), elevated sedimentation rate, low hemoglobin, dcSSc, or skin involvement of the trunk.

An important barrier in the study of SSc continues to be the difficulty in measuring disease activity.

In 2001, the Valentini Scleroderma Disease Activity Index was developed using multicenter data from 290 sequential patients fulfilling criteria for SSc and enrolled through the European Scleroderma Study Group [33]. It consists of 10 weighted variables: modified Rodnan skin score more than 14, scleredema, digital necrosis, arthritis, DLCO less than 80%, ESR more than 30 mm/h, hypocomplementemia (low C3 and/or C4), and worsening cardiopulmonary, skin and vascular symptoms in the past month as reported by the patient. The final score ranges from 0 (no activity) to 10 (very active). To date, however, this index has not yet undergone prospective evaluation.

In the future, presence or absence of these independent prognostic values may allow stratification of mortality and/or enrollment and randomization in clinical trials independently of just the currently accepted limited versus diffuse SSc classification.

Key points

- Systemic sclerosis is the leading indication for autologous hematopoietic stem cell transplantation (HSCT) of rheumatological diseases and over 250 patients have undergone this procedure.
- Autologous HSCT is so far the most effective therapy in reversing skin fibrosis and improvement in skin thickness has been shown to correlate with a better prognosis.
- Significative stabilization of internal organs' function has been observed for up to 5 years post-HSCT.
- The procedure seems feasible and well tolerated in selected candidates with no compromised cardiac function and before irreversible lung fibrosis takes place.
- Nonmyeloablative regimens are safer than myeloablative ones that include total body irradiation, especially in risk of treatment-induced malignancies.
- The first safety and efficacy results from phase II/III randomized clinical trials will be shortly available.

Standard immune-suppressive therapy

A definitive answer to the question of whether immune-suppressive medications benefit patients with SSc is not available despite widespread and decades-long history of clinical usage. Immune modulating and suppressive medications such as prednisone, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, and chloroquine are, in fact, commonly used for patients with diffuse SSc and overlap syndrome. However, randomized trials that support statistically significant improvement are generally nonexistent. In two small randomized trials [34,35] of 29 and 70 patients, respectively, methotrexate was not significantly better than placebo in improving skin score or pulmonary function. D-penicillamine demonstrated no improvement in skin score in a randomized double-blinded trial [36]. Rituximab has shown some encouraging results in improving lung function in a Greek randomized study [37•], involving, however, only 14 patients. Randomized trials of azathioprine, chloroquine, mycophenolate mofetil or cyclosporine versus placebo have not been reported.

Besides increasing risk of infection, two immune modulating medications, corticosteroids and especially cyclosporine, have been reported to precipitate renal crisis [38,39]. The immune-suppressive drug most commonly used for diffuse SSc and/or for SSc-related interstitial lung disease (ILD) is cyclophosphamide, administered either orally or intravenously (i.v.). It is the only immune-suppressive drug with reports of short-term efficacy in randomized trials and in SSc-related ILD [40–42]. However, the efficacy of cyclophosphamide in SSc-ILD, which has been descibed as 'modest benefit', must be taken in context. The term 'modest benefit' used in the publication of the Cyclophosphamide versus Placebo in Scleroderma Lung Disease Study [40] did not mean that lung function improved; in fact the lung function declined or worsened over 12 months in patients receiving cyclophosphamide. The 'modest benefit' meant that the lung function just declined less compared with placebo over a 12-month interval. Furthermore, by 2 years the decline in lung function was no different for cyclophosphamide than for placebo [41].

A recent meta-analysis systematically reviewed the effect of cyclophosphamide treatment on pulmonary function in patients with SSc and ILD. Three randomized clinical trials and six prospective observational studies with at least 12 months' follow-up were included for analysis. Based on improvement defined as at least 10% increase in DLCO or FVC, cyclophsophamide treatment in patients with SSc-related ILD did not result in clinically significant improvement of pulmonary function. In summary, even cyclophosphamide, the one immune-suppressive medication, generally considered most effective for SSc, lacks convincing data from randomized trials to unequivocally demonstrate its efficacy [43]. Despite lack of convincing evidence-based

Table 1 Independent predictors of mortality in systemic sclerosis by multivariate analysis

Author	No. of patients	Statistical method/how results reported	Independent predictors of mortality	Results[a]
Wynn *et al.* [14]	64	Cox regression analysis/risk ratio	S3 gallop; Aage at onset (70 years versus 20 years old)	5.4 ($P=0.0037$); 20 ($P=0.0017$)
Zarafonetis *et al.* [15]	390	Cox proportional hazards model/coefficient	Heart involvement (abnormal EKG, pericardial effusion or CHF by CXR)	2 ($P=0.01$)
Bulpitt *et al.* [19]	48	Stepwise Cox proportional hazards analysis/hazards ratio (95% CI)	Abnormal urine sediment	4.57 (1.48–14.1)
Nagy and Czirják [7]	171	Cox proportional hazards regression analysis with time-dependent data/risk ratio ($Pr > \chi^2$)	SRC; Pigmentation disturbances; CHF; Anemia (Ht $<33\%$) Respiratory failure	9.38 (0.01); 6.15 (0.01); 10.71 (0.03); 7.49 (0.01) ; 37.8 (0.01)
Bryan *et al.* [5]	280	Logistic regression model /odds ratio (95% CI)	Proteinuria; ESR $\geq$25; DLCO $\leq$70%	23.6 (1.9–298.6) 7.4 (2.6–21.2) 8.8 (1.8–44.5)
Clements *et al.* [22]	134	Stepwise multivariate logistic regression/odds ratio (95% CI)	Lung involvement mRSS $>$20	6.1 (1.6–23.1); 3.7 (1.2–11.7)
Jacobse *et al.* [9]	174	Cox regression analysis/Relative risk (95% CI)	Right heart failure; dcSSc; SRC; DLCO $<$40%	12.4 (2.5–60); 7.8 (1.8–35); 6.1 (1.8–21); 4.8 (1.1–20)
Ferri *et al.* [3]	1012	Cox proportional hazards model/Hazards ratio (95% CI)	lcSSc; dcSSc; SRC	2.88 (1.43–2.40) 4.89 (1.43–2.40) 3.76 (2.61–5.43)
Scussel-Lonzett *et al.* [4]	309	Stepwise Cox proportional hazards analysis/hazards ratio (95% CI)	Trunk involvement; DLCO $\leq$70%; Increased ESR $\geq$25 mm/h; Hemoglobin $\leq$12.5 g/dL	3.6 (1.57–8.3); 2.88 (1.43–5.8) 3.89 (1.68–8.95); 2.37 (1.15–4.87)
Simeon *et al.* [17]	79	Cox proportional hazards model/incidence density ratio (95% CI)	Age at diagnosis over 60 year; FVC $<$70%SRC	24.7 (2.9–205.1); 22.2 (4.4–111.7); 45.9 (6.4–331.6)
Nagy and Czirják [8]	80	Cox proportional hazards regression analysis with baseline data/risk ratio (95% CI)	SRC; Pericarditis; PIIINP; dcSSc	2.27 (0.51–10.11); 2.31 (0.42–12.7); 5.65 (1.39–23.04); 3.53 (0.84–14.84)
Czirják *et al.* [13]	366	Stepwise Cox proportional hazards model/Risk ratio (95% CI)	Increased ESR; SRC; dcSSc; Early malignancy	3.00 (1.83–4.93) 3.38 (1.87–6.10) 2.37 (1.49–3.78) 3.20 (1.62–6.32)
Hachulla *et al.* [28]	546	Stepwise Cox proportional hazards analysis/hazards ratio (95% CI)	PAH (mean PA $>$25mmHg at rest or $>$30mmHg during exercise); mRSS (per 1 point)	7.246 (4–13.2); 1.05 (1.02–1.06)
Beretta *et al.* [29]	558	Cox proportional hazards model/hazard ratios (95% CI)	Male sex; Age at diagnosis over 45 year; Renal involvement; DLCO $<$55%	3.01(1.66 – 5.45); 3.08 (1.59–5.97); 4.40 (2.22– 8.74); 2.56 (1.57– 4.29)
Tyndall *et al.* [30••]	5860	Stepwise Cox proportional hazards model/hazard ratios (95% CI)	Proteinuria; PAH	3.34 (2.11–5.28); 2.01 (1.44 2.82)
Kuo *et al.* [31]	1479	Multiple Cox regression analysis/hazard ratios (95% CI)	ESRD; male sex; cancer	2.59 (1.14–5.90); 1.60 (1.19–2.14); 2.71 (1.27–5.76)

BP, blood pressure; CHF, congestive heart failure; CXR, chest x ray; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, carbon monoxide lung diffusion; ESR, erythrocyte sedimentation rate; ESRD, end stage renal disease; FVC, forced vital capacity; Ht, hematocrit; icSSC, intermediate cutaneous systemic sclerosis; mRSS, modified Rodnan skin score; PAH, pulmonary artery hypertension; PIIINP, amino terminal propeptide of type III procollagen; RF, renal failure; SRC, scleroderma renal crisis. Adapted from [32].

[a] Only listed if more than 2.

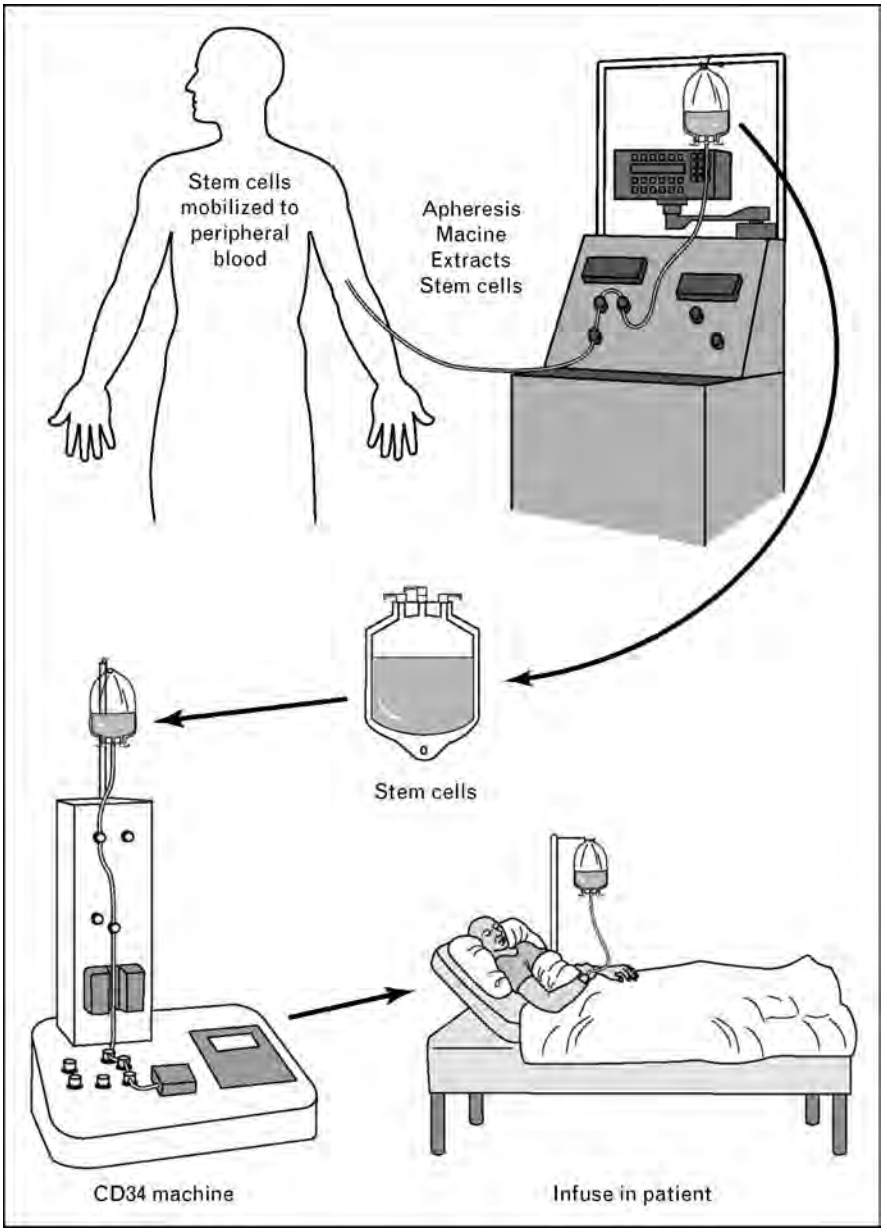
literature, immune-suppressive medications are commonly employed to treat SSc [44,45].

Methods of autologous hematopoietic transplantation for systemic sclerosis

Autologous hematopoietic stem cell transplantation (HSCT), although a well accepted term, is believed to be a misnomer by some, because there is no transplant, only infusion of an autologous blood product (the patient's own stem cells). Before receiving a transplant, patients with SSc receive 'conditioning' chemotherapy or radiation that destroys lymphocytes, subsequently; HSCs are infused to regenerate a new, hopefully self-tolerant, immune system (Fig. 1).

Hematopoietic stem cells are collected from the blood via outpatient leukapheresis. In order to mobilize sufficient stem cells into the blood to be harvested by leukapheresis, patients are treated with either cyclophosphamide and neupogen [granulocyte-colony stimulating factor (G-CSF)] or G-CSF alone. The Europeans and Chicago groups mobilize stem cells by i.v. infusion of cyclophosphamide (either 2 or 4 g/m^2) over 1–2 h, followed by

Figure 1 Hematopoietic stem cells are collected from peripheral blood



With permission from 'multiple sclerosis therapeutics third edition' by Jeffrey A. Cohen, Richard A. Rudick, Cambridge University, 2007.

G-CSF 5–10 μg/kg beginning 5 days later, and collection of stem cells 10 days after cyclophosphamide. Mobilization with cyclophosphamide and G-CSF provides a cyclophosphamide-related treatment ameliorating affect. Cyclophosphamide-induced lymphopenia also provides a partial in-vivo purge of lymphocytes. However, cyclophosphamide-induced neutropenia occurring 8–9 days after infusion requires judicious monitoring for infections. The Seattle group avoids neutropenia by collecting stem cells using only daily G-CSF 16 μg/kg and corticosteroids with leukapheresis on the 4th or 5th day of neupogen. Daily oral steroids are administered to minimize neupogen-induced disease flare, which in SSc manifests as telangiectasias and arthralgias.

The term peripheral blood stem cells (PBSC) is used to describe the mobilized leukapheresis product. PBSCs are a collection of mononuclear cells including progenitor (stem) cells and lymphocytes and may be cryopreservated without further purification or undergo CD34 selection to further reduce lymphocytes from the product before cryopreservation. It remains unclear whether the collected PBSCs (or bone marrow) should be lymphocyte depleted (usually by means of a commercially available instrument that positively selects for CD34 + progenitor cells) before reinfusion of the autograft. T-cell depletion (TCD) of the autograft does increase the risk of late opportunistic infections, especially life-threatening viral infections such as cytomegalovirus and Epstein–Barr virus [46,47]. The argument in favor of TCD is that it may minimize reinfusion of autoreactive lymphocytes that could lead to early relapse. The argument against taking the increased infectious risk from a TCD graft is that complete lymphoablation may not be necessary to induce long-term remission.

Rationale of autologous hematopoietic transplantation for systemic sclerosis

The hematopoietic stem cell is also the 'immune' stem cell, differentiating into mature T-lymphocytes, B-lymphocytes, macrophages, and dendritic cells. Autologous hematopoietic stem cell transplantation is a form of intense immune-suppressive therapy: the transplant-conditioning regimen ablates the aberrant disease-causing immune cells resulting in an immediate immune cease fire.

The manner in which antigen is presented helps determine the immune response, that is, presentation of antigen without costimulation (without inflammation) biases the immune system toward anergy [48]. The hematopoietic stem cells then regenerate, within a noninflammatory environment, a new immune system, hopefully tolerant [49]. HSCT is designed to favorably alter the inflammatory and autoimmune component of SSc but not directly alter SSc-related vasculopathy, unless SSc-related vasculopathy is also immune-mediated.

It has previously been demonstrated that an immune reset with regeneration of thymic-derived naive T cells occurs after autologous HSCT for autoimmune diseases such as multiple sclerosis. However, the observed persistence posttherapy of some pre-existing T-cell clones suggested the potential for disease recurrence [50]. Moreover, in patients with lupus, two immune studies [51,52] indicated an immunologic remission following transplant.

Data on immune reconstitution on 11 patients with SSc who underwent HSCT with purified CD34(+) after high dose Cy conditioning documented aTh1/Th2 ratio significantly increased for at least 3 years after HSCT. Notably, improvement of skin sclerosis was significantly associated with the change in the serum anti-Scl-70 at 36 months after HSCT [53•]. Bohgaki *et al.* [54] analyzed the relationship between clinical benefits and immunological changes in 10 patients with SSc treated with high-dose cyclophosphamide followed by highly purified CD34+ cells ($n = 5$) or unpurified grafts ($n = 5$). Clinical and immunological findings were similar between good and poor responders, or CD34-purified and unpurified groups at inclusion. The authors suggest that immunosuppression sufficient to downregulate thymic function, rather than the graft manipulation, can lead to clinical benefits in patients with SSc. Additionally, the signal joint T-cell receptor rearrangement excision circles (sjTREC) values were significantly suppressed at 3 months after autologous HSCT in good responders compared with poor responders with the investigators suggesting that appropriate monitoring of sjTREC values may predict clinical benefits in transplanted SSc.

Conditioning regimen

The toxicity and efficacy of an autologous HSCT are entirely a consequence of the conditioning regimen. In practice, there are currently two philosophical approaches to the conditioning regimen, namely nonmyeloablative versus myeloablative [49]. The latter (utilized by the Seattle/NIH consortium) are based on myeloablative cancer drugs and/or total body irradiation (TBI); in particular, the myeloablative regimen for SSc employs TBI with lung and kidney shielding. These extreme regimens cause irreversible bone marrow failure, thus requiring mandatory HSC reinfusion to recover. In contrast, nonmyeloablative regimens (utilized by the Europeans and Chicago) are designed to maximally suppress the immune system without destruction of the bone marrow stem cell compartment. Recovery from nonmyeloablative conditioning regimen cytopenias will occur without reinfusion of stem cell. The infused stem

cells, while not necessary for recovery, shorten the interval of neutropenia and duration of hospitalization.

In addition to patient safety benefits from lower toxicity, nonmyeloablative regimens are less expensive, and less likely to be associated with late complications such as infertility or secondary solid tumors, myelodysplastic syndrome/leukemias [55–57].

The risk of second cancer may be even higher in SSc patients exposed to TBI because cells from SSc patients have, for unclear reasons, a high incidence of increased genetic instability with abnormal chromosome fragility and breakage compared with the general population [58–63]. Current data for transplant of autoimmune diseases support the concept that nonmyeloablative regimens have lower mortality when compared with myeloablative regimens [48]. However, randomized comparisons between regimens concerning long-term disease response, survival, and late toxicities such as regimen-related second malignancies have not been performed in patients with SSc.

Phase I-II trials of hematopoietic stem cell transplantation for systemic sclerosis

Autologous HSCT has generally been restricted to patients with diffuse SSc, although occasionally limited SSc with lung involvement has been included [32,64–71] (Table 2). Nonmyeloablative regimens utilize cyclophosphamide with or without antithymocyte globulin (ATG) whereas myeloablative regimens are composed of cyclophosphamide, ATG, and TBI with pulmonary and renal shielding. These initial trials were complicated by high-treatment-related mortality (TRM) (Table 3) [32,64–71], although nonmyeloablative regimens are less toxic. It is also generally recognized that with experience, exclusion of high-risk candidates, exclusion of patients with scleroderma-related cardiac dysfunction, and referral and treatment of patients early in disease course instead of relegating transplant to salvage therapy for end-stage disease, the procedure is safer.

TBI was initially accompanied by exacerbation of pulmonary hypoxia and pulmonary deaths as well as precipitation of renal crises leading to subsequent patients receiving both lung and kidney shielding during TBI exposure [66]. Some patients, independent of myeloablative or nonmyeloablative intent, died of cardiac failure, leading to the need for careful pre-enrollment cardiac evaluation and making patients with compromised cardiac function ineligible. Pulmonary artery hypertension [pulmonary artery systolic pressure (PASP) more than 40 mmHg], pericardial effusion more than 1 cm on chest computed tomography (CT) [72], evidence of constrictive pericarditis, and tricuspid peak systolic excursion less

Table 2 Autologous hematopoietic transplantation in systemic sclerosis: phase I/II studies

Author	Center (No. of sites)	No. of patients	Mean age (years)	Disease subset	Mobilization	Cell selection	Conditioning regimen
Mixed regimens							
Binks *et al.* [64]	Multi (18)	41	41	37 dSSc; 4 lSSc	Cy + G-CSF or; G-CSF	Mixed	Mixed
Farge *et al.* [65]	Multi	11	42	NA	Cy 4 g/m2 + G-CSF	Yes	Cy 200 mg/kg or melphalan 140 mg/m^2
Myeloablative regimens							
Mcsweeney *et al.* [66]	Multi (4)	19[b]	40	NA	G-CSF	Yes	TBI 800 cGy ± lung shielding + 120 mg/kg Cy + eATG 90 mg/kg
Nash *et al.* [67]	Multi (5)	34[c]	41	NA	G-CSF	Yes	TBI 800 cGy + lung shielding + 120 mg/kg Cy + eATG 90 mg/kg
Nonmyeloablative regimen							
Farge *et al.* [68]	Multi (22)	57[a]	40	50 dSSc; 4 lSSc; 3 NS	Cy + G-CSF or; G-CSF	mixed (yes 87%)	Cy 150–200 mg/kg (61%) or Cy 200 + ATG (21%)
Tsukamoto *et al.* [69]	Single	6	54	NA	Cy 4 g/m2 2 + G-CSF	Yes	Cy 200 mg/kg
Oyama *et al.* [70]	Single	10	47	9 dSSc1 lSSc	Cy 2 g/m2 + G-CSF	No	Cy 200 mg/kg + 7.5 mg/kg rATG
Vonk *et al.* [71]	Multi (3)	26	42	DSSc	Cy 4 g/m2 + G-CSF	Yes	Cy 200 mg/kg

Cy, cyclophosphamide; dSSc, diffuse cutaneous systemic sclerosis; eATG, equine antithymocyte globulin; G-CSF, granulocyte-colony stimulating factor; lSSc, limited systemic sclerosis; NA, not available; rATG, rabbit antithymocyte globulin; TBI, total body irradiation. Adapted from [32].

[a] Thirty-two patients previously reported in Binks 2001.

[b] Eight patients previously reported Binks 2001.

[c] Eleven patients previously reported in Mcsweeney 2002.

Table 3 Hematopoietic transplantation in systemic sclerosis: outcome of phase I/II studies

Author	Skin score	Pulmonary function tests	Overall mortality /TRM	Survival
Mixed regimens				
Binks *et al.* [64]	Improved in 69%	FVC and TLC no change	27/17%	73% at 1 year
Farge *et al.* [65]	Improved in 66%	No change	36/9.1%	NA
Myeloablative regimen				
Mcsweeney *et al.* [66]	Improved in 100%	Worse at 3 months then return to baseline	21/15%	79% at 2 years
Nash *et al.* [67]	Improved in 70%	Increased FVC/decreased DLCO	36/23%	64% at 5 years
Non-myeloablative regimens				
Farge *et al.* [68]	Improved in 70% at 6 months; 66% at 12 months; 78% at 24 months; 60% at 36 months	No change	23/8.7%	72% at 5 years
Tsukamoto *et al.* [69]	Improved in 100% at 12 months	Improved in PaO_2 and HRCT	0%	100%
Oyama *et al.* [70]	Improved in 100% but 20% relapse	No change	10/0%	90%
Vonk *et al.* [71]	Improved in 73% at 1 year and 94% at 5 years	No change	8/0%	96% at 5 year

Improvement in skin score is decline in modified rodnan skin score (mRSS) by at least 25%. FVC, forced vital capacity; HRCT, high-resolution chest computed tomography; NA, not available; TLC, total lung capacity; TRM, treatment related mortality. Adapted from [32].

than 1.8 cm [73] should be considered exclusion criteria for transplantation.

The current outcome data (Table 3) [64–71] indicate that HSCT is the single most effective therapy for improving skin flexibility, that is, improving skin score [decreasing modified Rodnan skin score (mRSS) by 25% or more]. Improved skin score correlates with increased mobility and functionality of hands and joints [74] as well as improved quality of life [67,71]. This improvement is usually noticeable before hospital discharge and often continues for years after the transplant (although relapse may occur). Because nontransplant studies suggest that improvement in skin score correlates with improved survival [38,40], it is anticipated that improved skin score following autologous HSCT may translate into improved survival. Stabilization of internal organ function has been observed for up to 5 years after HSCT [71].

Despite some dramatic improvements in high-resolution CT of the lung in some patients, the procedure did not demonstrate significant improvement in pulmonary function. To date, improvement by at least a mean of 10% of total lung capacity, FVC or oxygen diffusion capacity determined by DLCO has not been reported, and in some cases these measures have deteriorated compared with baseline. It is important for future studies to minimize further pulmonary injury from the transplant regimen. TBI, even with lung shielding, may blunt improvement in posttransplant pulmonary function due to radiation-related pneumonitis. ATG causes a first pass cytokine release syndrome [75,76] that may also induce lung injury and pulmonary edema that can be minimized by reduction in the first dose of rATG (0.5 mg/kg or less) and pretreatment with high-dose solumedrol. A Japanese study [77•] showed that several CT findings [presence of honeycombing, extent of ground glass opacity (GGO), and early change in extent of GGO] and pretreatment KL-6 may be useful to discriminate between responder and nonresponder in 15 patients who received auto-PBSCT for interstitial pneumonia SSc-associated.

Although autologous HSCT was designed to arrest inflammation/autoimmunity in patients with SSc, even with myeloablative TBI-containing regimens, serologic remissions have not occurred. Titers may initially decline, but patients remain positive for antitopoisomerase I as well as other SSc-associated antibodies. It remains unclear if antibody titer rebound will be a harbinger of clinical relapse. Because initial studies focused on skin, quality of life, and pulmonary function, there are no data on posttransplant changes in pulmonary artery hypertension (PASP), cardiac performance, or gastrointestinal function (patulous esophogous, intestinal peristalis, or gastric antral vascular ectasia) (Table 3) [64–71].

Cutaneous fibrosis has been confirmed histologically to resolve following transplant. Verrecchia *et al.* [78] demonstrated in five of the 12 SSc patients whose biopsies were available pre-HSCT and post-HSCT that the histological extent of skin fibrosis correlates closely with the mRSS and that they both regress after autologous HSCT. Moreover, the extent of TGF-β-signalling activation and resulting gene expression in SSc skin fibroblasts appear to parallel the severity of the disease. Microcapillary regeneration also occurs following transplant using either myeloablative or regimens. In an Italian study [79] at 3 months after nonmyeloablative HSCT, the Nailfoild video capillaroscopy (NVC) pattern changed from 'late' into 'active', and this pattern was still present 1 year after HSCT. In patients treated with only CYC, instead, no NVC modifications were observed during 24 months of follow-up and the pattern always remained 'late'. A recent study [80] performed on skin biopsies of seven scleroderma patients using immunohistochemical and

mRNA in-situ hybridization techniques together with morphometry before and after transplant also suggested that HSCT induces neoangiogenesis, supporting these findings. Nevertheless, although generally not reported, Raynaud's phenomena persists, although often with subjective improvement in frequency and severity after autologous transplantation.

Randomized trials

The results achieved in the phase I-II studies formed the basis for three prospective randomized autologous HSCT trials (Table 4) [32,81–83]. All the trials have simllar eligibility criteria, endpoints and control treatment, allowing an easy future comparison. Two trials are non-myeoablative [Autologous Stem cell Transplantation International Scleroderma (ASTIS), American Systemic Sclerosis Immune Suppression versus Transplant (ASSIST)], whereas one uses a TBI-based myeloablative regimen [Scleroderma Cyclophosphamide versus Transplant (SCOT)]. Two trials CD34 select the graft (ASTIS, SCOT) and one does not (ASSIST). Two trials are survival studies and do not allow cross over to transplant for progression on the control arm (ASTIS, SCOT). One trial is a treatment failure study rather than survival study and, therefore, allows cross over to transplant for disease progression (ASSIST). Two trials are multicenter (ASTIS, SCOT) randomized phase III studies, whereas one is a single center study (ASSIST) randomized phase II [81–83].

Table 4 Prospective randomized clinical trials ongoing in systemic sclerosis

RCT	Inclusion criteria	HSCT	Control arm
ASTIS [81]	dcSSc with: (a) disease duration $\leq$4 years and mRSS $\geq$15 and one of the following: Respiratory involvement = DLCO and/or FVC <80% and evidence of ILD (by CXR and/or HR-CT scan and/or BAL and/or biopsy of the lungs) Renal involvement = persistent urinalysis abnormalities or microangiopathic hemolytic anemia or new renal insufficiency Cardiac involvement = reversible CHF or arhythmia or pericardial effusion (b) Disease duration <2 years plus mRSS $\geq$20 plus involvement of trunk plus ESR > 25 mm/1st hour and/or Haemoglobin <11 g/dL	Mobilization: Cy 4 g/m^2 and G-CSF Conditioning: Cy 200 mg/kg and rATG 7.5 mg/kg Graft manipulation: CD34 selection	Cy 750 mg/m2 IV pulse monthly for 12 months Cross over to HSCT: not allowed
SCOT [82]	dcSSc and disease duration $\leq$5 years and mRSS $\geq$16 and one of the following: Respiratory involvement = DLCO and/or FVC <70% *and* evidence of ILD (by HR-CT scan and/or BAL) Renal involvement = history of SSc related renal crisis or disease not active	Mobilization: G-CSF Conditioning: TBI 800 cGy (with bilateral lung and kidney shielding) Cy 120 mg/kg plus eATG 90 mg/kg Graft manipulation: CD34 selection	Cy 750 mg/m2 IV pulse monthly for 12 months Cross over to HSCT: not allowed
ASSIST [83]	dcSSc with: (a) Disease duration $\leq$4 years and mRSS $\geq$14 and one of the following: Respiratory involvement = DLCO <80% or decrease in lung function $\geq$10% over 12 months or Active alveolitis on BAL or evidence of ILD (by CXR and/or HR-CT scan and/or BAL) Renal involvement = two or more of the following: proteinuria, hematuria, a diastolic BP >95 mm/hg. Cardiac involvement = abnormal EKG GI involvement = confirmed on radiological study OR lcSSc with above pulmonary involvement	Mobilization: Cy 2 g/m^2 and G-CSF Conditioning: Cy 200 mg/kg plus rATG 6.5 mg/kg Graft manipulation: no CD34 selection	Cy 1 g/m2 IV pulse monthly for 6 months Cross over to HSCT: allowed after 12 months if there is worsening >25% in mRSS or >10% deterioration in FVC or DLCO

ASSIST, American scleroderma stem cell versus immune suppression trial; ASTIS, Autologous stem cell transplantation international scleroderma; ATG, rabbit antithymocyte globulin; BAL, bronchoalveolar lavage; BP, blood pressure; CHF, congestive heart failure; CXR, chest x ray; Cy, cyclophosphamide; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, carbon monoxide lung diffusion; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; ILD, interstitial lung disease; IV, intravenous infusion; mRSS, modified Rodnan skin score; RCT, randomized clinical trial; SCOT, scleroderma cyclophosphamide or transplantation. Adapted from [32].

The ASTIS trial was launched in Europe in 2001 and enrollment has now been completed. One hundred and fifty-six patients have been randomized to either high-dose immunoablation followed by autologous stem cell transplantation (79 patients) or pulse-therapy cyclophosphamide i.v (77 patients). The TRM in the transplant group was 5.7% (4 of 79) versus 0% in the control group (Farge *et al*. [28,55,64,65,68,71,72,78], personal communication). The efficacy results of this trial are expected to become available shortly. The SCOT trial, started in 2005, is being sponsored by the National Institutes of Health and is still recruiting patients. The ASSIST trial, conducted at Northwestern University (Chicago), has been concluded and publication is pending. These trials will be important to clarify the safety and efficacy of this procedure for patients with SSc, to compare early and late toxicity (second malignancies) from the different regimens, to determine the benefit, if any, from CD34 selection of the autograft, and to allow comparison of safety from multiple centers versus a single experienced center of excellence (Table 4) [81–83].

Conclusion

SSc is a debilitating disease that is still poorly understood and with a challenging management. Patients with dcSSc or internal organ involvement have a poor prognosis with high mortality. To date, no therapy has been shown to reverse the natural course of the disease. Standard immune suppressive drugs are commonly utilized to treat patients, but randomized trials have generally failed to demonstrate any long-term benefit. SSc is the leading indication for autologous HSCT of rheumatological diseases and over 250 patients with SSc have undergone this procedure.

Autologous HSCT is the most effective therapy in reversing skin fibrosis. It is noteworthy that the extent and severity of skin involvement have been recognized to correlate with internal organ involvement, and on the contrary, improvement in skin thickness correlates with improvement in survival [26,27]. Stabilization of internal organ function has also been observed for up to 5 years post-HSCT. Nonmyeloablative regimens are safer than myeloablative ones that include TBI, especially in risk of treatment-induced malignancies [49]. TRM was reduced by better pretransplant evaluation to exclude patients with compromised cardiac function and by treating patients earlier in disease, allowing selected patients the option of autologous HSCT treatment The first results from phase II/III randomized clinical trials will be shortly available.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 620–621).

1 LeRoy EC, Black C, Fleischmajer R, *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15:202–205.

2 Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, *et al.* Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med 2005; 118:2–10.

3 Ferri C, Valentini G, Cozzi F, *et al.* Systemic sclerosis: demographic, clinical, and serologic features and survival in 1012 Italian patients. Medicine(Baltimore) 2002; 81:139–153.

4 Scussel-Lonzetti L, Joyal F, Raynauld JP, *et al.* Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine (Baltimore) 2002; 81:154–167.

5 Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. Arthritis Rheum 1999; 42:2660–2665.

6 Czirják L, Nagy Z, Szegedi Gy. Survival analysis of 118 patients with systemic sclerosis. J Intern Med 1993; 234:335–337.

7 Nagy Z, Czirják L. Predictors of survival in 171 patients with systemic sclerosis (scleroderma). Clin Rheumatol 1997; 16:454–460.

8 Nagy Z, Czirják L. Increased C reactive protein and aminoterminal propeptide of type III procollagen levels are unfavourable predictors of survival in systemic sclerosis (scleroderma). Clin Exp Rheumatol 2005; 23:165–172.

9 Jacobsen S, Ullman S, Shen GQ, *et al.* Influence of clinical features, serum antinuclear antibodies, and lung function on survival of patients with systemic sclerosis. J Rheumatol 2001; 28:2454–2459.

10 Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis 1998; 57:682–686.

11 Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998; 37:750–755.

12 Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum 2010; 39:269–277.

13 Czirják L, Kumánovics G, Varjú C, *et al.* Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Ann Rheum Dis 2008; 67:59–63.

14 Wynn J, Fineberg N, Matzer L, *et al.* Prediction of survival in progressive systemic sclerosis by multivariate analysis of clinical features. Am Heart J 1985; 110:123–127.

15 Zarafonetis CJ, Dabich L, Negri D, *et al.* Retrospective studies in scleroderma: effect of potassium para-aminobenzoate on survival. J Clin Epidemiol 1988; 41:193–205.

16 Medsger TA Jr, Masi AT. Survival with scleroderma II. A life-table analysis of clinical and demographic factors in 358 male U.S. veteran patients. J Chron Dis 1973; 26:647–660.

17 Simeon CP, Armadans L, Fonollosa V, *et al.* Mortality and prognostic factors in Spanish patients with systemic sclerosis. Ann Rheum Dis 2003; 42:71–75.

18 Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000; 43:2437–2444.

19 Bulpitt KJ, Clements PJ, Lachenbruch PA, *et al.* Early undifferentiated connective tissue disease: III. Outcome and prognostic indicators in early scleroderma (systemic sclerosis). Ann Intern Med 1993; 118:602–609.

20 Farmer RG, Gifford RW, Hines EA. Prognostic significance of Raynaud's phenomenon and other clinical characteristics of systemic scleroderma. Circulation 1960; 21:1088–1095.

21 Geirsson ÁJ, Wollheim FA, Akesson A. Disease severity of 100 patients with systemic sclerosis over a period of 14 years: using a modified Medsger scale. Ann Rheum Dis 2001; 60:1117–1122.

22 Clements PJ, Hurwitz EL, Wong WK, *et al.* Skin thickness score as a predictor and correlate of outcome in systemic sclerosis. Arthritis Rheum 2000; 43:2445–2454.

23 Majewski S, Wojas-Pelc A, Malejczyk M, *et al.* Serum levels of soluble TNF alpha receptor type I and the severity of systemic sclerosis. Acta Derm Venereol 1999; 79:207–210.

24 Giordano M, Valentini G, Migliaresi S, *et al.* Different antibody patterns and different prognosis in patients with scleroderma with various extent of skin sclerosis. J Rheumatol 1986; 13:911–916.

25 Tamaki T, Mori S, Takehara K. Epidemiological study of patients with systemic sclerosis in Tokyo. Arch Dermatol Res 1991; 283:366–371.

26 Shand L, Lunt M, Nihtynova S, *et al.* Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis. Application of a latent linear trajectory model. Arthritis Rheum 2007; 56:2422–2431.

27 Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum 2001; 44:2828–2835.

28 Hachulla E, de Groote P, Gressin V, *et al.* The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009; 60:1831–1839.

29 Beretta L, Santaniello A, Cappiello F, *et al.* Development of a five-year mortality model in systemic sclerosis patients by different analytical approaches. Clin Exp Rheumatol 2010; 28 (2 Suppl 58):S18–S27.

30 •• Tyndall AJ, Bannert B, Vonk M, *et al.* Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010; 69:1809–1815.

The EULAR scleroderma trials and research (EUSTAR) database represents the largest prospective SSc cohort in which risk factors and cause for deaths have been analyzed. In this study disease-related causes, in particular pulmonary fibrosis, PAH and cardiac causes, accounted for the majority of deaths.

31 Kuo CF, See LC, Yu KH *et al.* Epidemiology and mortality of systemic sclerosis: a nationwide population study in Taiwan. Scand J Rheumatol 2011. [Epub ahead of print].

32 Milanetti F, Bucha J, Testori A, Burt RK. Autologous hematopoietic stem cell transplantation for systemic sclerosis. Curr Stem Cell Res Ther. 2011; 6:16–28.

33 Valentini G, Della Rossa A, Bombardieri S, *et al.* European multicentre study to define disease activity criteria for systemic sclerosis II. Identification of disease activity variables and development of preliminary activity indices. Ann Rheum Dis 2001; 60:592–598.

34 Pope JE, Bellamy N, Seibold JR, *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum 2001; 44:1351–1358.

35 Van den Hoogen FH, Boerbooms AM, Swaak AJ, *et al.* Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24-week randomized double-blind trial, followed by a 24-week observational trial. Br J Rheumatol 1996; 35:364–372.

36 Clements PJ, Furst DE, Wong WK, *et al.* High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. Arthritis Rheum 1999; 42:1194–1203.

37 • Daoussis D, Liossis SN, Tsamandas AC, *et al.* Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford) 2010; 49:271–280.

This is the first randomized study to show that an immunomodulator drug, beside cyclophosphamide, may significantly improve lung function in SSc patients. The median percentage of improvement of FVC in the rituximab (RTX) group was 10.25%, whereas that of deterioration in the controls was 5.04%. Similarly, the median percentage of improvement of DLCO in the RTX group was 19.46%, whereas that of deterioration in the control group was 7.5%.

38 Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998; 41:1613–1619.

39 Clements PJ, Sterz M, Danovitch G, *et al.* Cyclosporin (CsA) in systemic sclerosis (SSc): results of a 48-week open safety study in 10 SSc patients. Arthritis Rheum 1993; 36:75–83.

40 Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006; 354:2655–2666.

41 Tashkin DP, Elashoff R, Clements PJ, *et al.* Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007; 176:1026–1034.

42 Nadashkevich O, Davis P, Fritzler M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. Clin Rheumatol 2006; 25:205–212.

43 Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. Arthritis Res Ther 2008; 10:R124.

44 Hunzelmann N, Moinzadeh P, Genth E, *et al.* High frequency of corticosteroid and immunosuppressive therapy in patients with systemic sclerosis despite limited evidence for efficacy. Arthritis Res Ther 2009; 11:R30.

45 Pope JE, Ouimet JM, Krizova A. Scleroderma treatment differs between experts and general rheumatologists. Arthritis Rheum 2006; 55:138–145.

46 Frère P, Pereira M, Fillet G, Beguin Y. Infections after CD34-selected or unmanipulated autologous hematopoietic stem cell transplantation. Eur J Haematol 2006; 76:102–108.

47 Kohno K, Nagafuji K, Tsukamoto H, *et al.* Infectious complications in patients receiving autologous CD34-selected hematopoietic stem cell transplantation for severe autoimmune diseases. Transpl Infect Dis 2009; 11:318–323.

48 Schwartz RH. T cell anergy. Annu Rev Immunol 2003; 21:305–334.

49 Burt RK, Loh Y, Pearce W, *et al.* J. Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases. JAMA 2008; 299:925–936.

50 Muraro PA, Douek DC, Packer A, *et al.* Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. J Exp Med 2005; 201:805–816.

51 Zhang L, Bertucci AM, Ramsey-Goldman R, *et al.* Regulatory T cell (TReg) subsets return in patients with refractory lupus following adult stem cell transplantation: TGF-b producing CD81 Treg (CD8TGF-b Treg) are associated with suppressing lupus into immunologic remission. J immunol 2009; 183:6346–6358.

52 Alexander T, Thiel A, Rosen O, *et al.* Depletion of autoreactive immunologic memory followed by autologous hematopoietic stem cell transplantation in patients with refractory SLE induces long-term remission through de novo generation of a juvenile and tolerant immune system. Blood 2009; 113:214–223.

53 • Tsukamoto H, Nagafuji K, Horiuchi T, *et al.* Analysis of immune reconstitution after autologous CD34+ stem/progenitor cell transplantation for systemic sclerosis: predominant reconstitution of Th1 CD4+ T cells. Rheumatology (Oxford) 2011; 50:944–952.

This study specifically addressed immune reconstitution in 11 SSc patients. HSCT with purified CD34(+) cells was effective in controlling the disease activity of SSc even if the majority of CD4(+) cells were memory but not naive T cells, and regulatory CD4(+) T cells were not recovered. Th1/Th2 ratio was significantly increased for at least 3 years after HSCT.

54 Bohgaki T, Atsumi T, Bohgaki M, *et al.* Immunological reconstitution after autologous hematopoietic stem cell transplantation in patients with systemic sclerosis: relationship between clinical benefits and intensity of immunosuppression. J Rheumatol 2009; 36:1240–1248.

55 Burt RK, Abinun M, Farge-Bancel D, *et al.* Risks of immune system treatments. Science 2010; 328:825–826.

56 Burt RK, Marmont A, Oyama Y, *et al.* Randomized controlled trials of autologous hematopoietic stem cell transplantation for autoimmune diseases: the evolution from myeloablative to lymphoablative transplant regimens. Arthritis Rheum 2006; 54:3750–3760.

57 Montoto S, Canals C, Rohatiner AZ, *et al.* Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. Leukemia 2007; 21:2324–2331.

58 Emerit I, Housset J, De Grouchy J, Carnus JP. Chromosomal breakage in diffuse scleroderma. A study of 27 patients. Europ J Clin Biol Res 1971; 16:683–694.

59 Pan SF, Rodnan GP, Seutsch M, Wald N. Chromosomal abnormalities in progressive systemic sclerosis (scleroderma) with consideration of radiation effects. J Lab Clin Med 1975; 86:300–308.

60 Rittner G, Schwanitz G, Baur MP, *et al.* Family studies in scleroderma (systemic sclerosis) demonstrating an HLA-linked increased chromosomal breakage rate in cultured lymphocytes. Hum Genet 1988; 81:64–70.

61 Migliore L, Bevilacqua C, Scarpato R. Cytogenetic study and FISH analysis in lymphocytes of systemic lupus erythematosus and systemic sclerosis patients. Mutagenesis 1999; 14:227–231.

62 Artlett CM, Black CM, Briggs DC, *et al.* Telomere reduction in scleroderma patients: a possible cause for chromosomal instability. Br J Rheumatol 1996; 35:732–737.

63 Wolff DJ, Needleman BW, Wasserman SS, Schwarts S. Spontaneous and clastogen induced chromosomal breakage in scleroderma. J Rheumatol 1991; 18:837–840.

64 Binks M, Passweg JR, Furst D, *et al.* Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. Ann Rheum Dis 2001; 60:577–584.

65 Farge D, Marolleau JP, Zohar S, *et al.* Autologous bone marrow transplantation in the treatment of refractory systemic sclerosis: early results from a French multicentre phase I-II study. Br J Haematol 2002; 119:726–739.

66 McSweeney PA, Nash RA, Sullivan KM, *et al.* High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. Blood 2002; 100:1602–1610.

67 Nash RA, McSweeney PA, Crofford LJ, *et al.* High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. Blood 2007; 110:1388–1396.

68 Farge D, Passweg J, van Laar JM, *et al.* Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. Ann Rheum Dis 2004; 63:974–981.

69 Tsukamoto H, Nagafuji K, Horiuchi T, *et al.* A phase I-II trial of autologous peripheral blood stem cell transplantation in the treatment of refractory autoimmune disease. Ann Rheum Dis 2006; 65:508–514.

70 Oyama Y, Barr WG, Statkute L, *et al.* Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with systemic sclerosis. Bone Marrow Transplant 2007; 40:549–555.

71 Vonk MC, Marjanovic Z, van den Hoogen FH, *et al.* Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. Ann Rheum Dis 2008; 67:98–104.

72 Snowden JAs, Saccardi R, M Allez S *et al.* Haematopoietic stem cell transplantation (HSCT) in severe autoimmune diseases (ADs): updated guidelines of the European Group for Blood and Marrow Transplantation (EBMT). Submitted.

73 Forfia PR, Fisher MR, Mathai SC, *et al.* Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 2006; 174:1034–1041.

74 Englert H, Kirkham S, Moore J, *et al.* Autologous stem cell transplantation in diffuse scleroderma: impact on hand structure and function. Intern Med J 2008; 38:692–696.

75 Taniguchi Y, Frickhofen N, Raghavachar A, *et al.* Antilymphocyte immunoglobulins stimulate peripheral blood lymphocytes to proliferate and release lymphokines. Eur J Haematol 1990; 44:244–251.

76 Wing M. Monoclonal antibody first dose cytokine release syndromes-mechanisms and prediction. J Immunotoxicol 2008; 5:11–15.

77 Yabuuchi H, Matsuo Y, Tsukamoto H, *et al.* Correlation between pretreatment • or follow-up CT findings and therapeutic effect of autologous peripheral blood stem cell transplantation for interstitial pneumonia associated with systemic sclerosis. Eur J Radiol 2011 [Epub ahead of print].
This is the first report on the serial CT change after immunosuppressive therapy for interstitial pneumonia with SSc. Moreover, it is the first study to analyze the pretreatment CT findings that could predict the therapeutic effect on interstitial pneumonia with SSc: honeycombing, extent of GGO, early change of the extent of GGO and pretreatment KL-6 may be useful to discriminate between responder and nonresponder in patients who received auto-PBSCT for interstitial pneumonia with SSc.

78 Verrecchia F, Laboureau J, Verola O, *et al.* Skin involvement in scleroderma—where histological and clinical scores meet. Rheumatology (Oxford) 2007; 46:833–841.

79 Miniati I, Guiducci S, Conforti ML, *et al.* Autologous stem cell transplantation improves microcirculation in systemic sclerosis. Ann Rheum Dis 2009; 68:94–98.

80 Fleming JN, Nash RA, McLeod DO, *et al.* Capillary regeneration in scleroderma: stem cell therapy reverses phenotype? PLoS ONE 2008; 3:e1452.

81 http://www.astistrial.com.

82 http://www.clinicaltrials.gov (NCT00114530).

83 http://www.clinicaltrials.gov (NCT00278525).