EBMT European Society for Blood and Marrow Transplantation

ASTIS and BEYOND…

we may improve conditioning and maintenance therapy
SSc organ involvement per se is the limit
patients selection and center expertise are critical

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www.mathec.com

ASTIS: 2001-2011

Pts rapidly progressive or severe SSc (n = 156)

- 4 yrs + skin score 15 (0-51) + involvement heart/lung/kidney
- 2 yrs + skin score 20 + ESR>25mm/1st hr and/or Hb<11 gr/dL

Immunoablation + AST =

1. **Mobilisation** *CYC4 g/m², G-CSF 10 m g/kg*
2. **Leukapheresis /CD34-selection**
3. **Conditioning** ***C YC 200 mg/kg, ATG 7.5 mg/kg***

Reinfusion CD34+ cells

Standard-therapy

12x monthly

i.v. pulse CYC 750 mg/m²

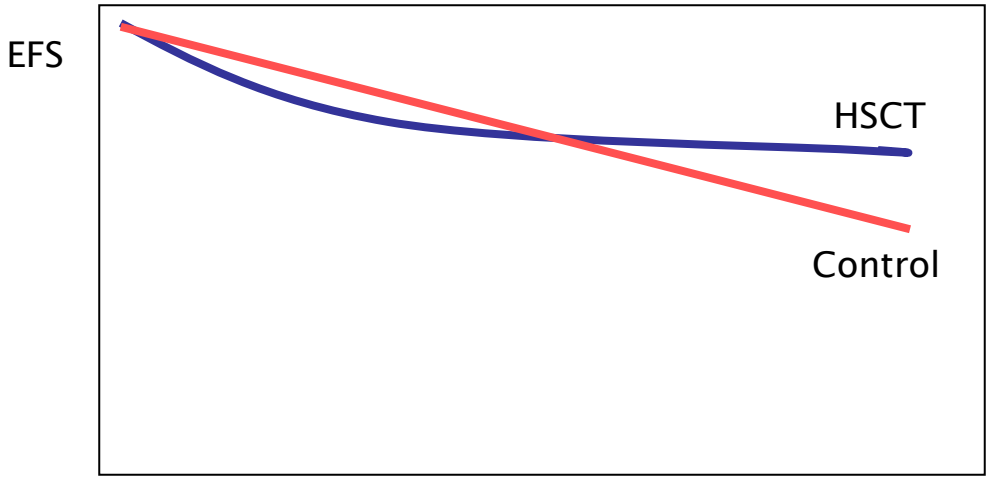
EFS = survival minus persistent major organ failure (heart, lung, kidney)

Exclusion criteria: PHT > 50 mmHg, DLCO < 40%, creat.cl. < 40 ml/min.
LVEF < 45%; uncontrolled arhythmia; cardiac tamponade
infection, etc. previous treatment with CYCLO: >5 gr iv, >3 mths po

Q. Does early intensive immunosuppression with HSCT improve outcome of patients with poor prognosis early diffuse cutaneous systemic sclerosis?

ASTIS trial December 2012 JvL*-DF*-AT (May 2012 data cut-off)

sample size 150 pts based on 10-yr accrual,
11-yr follow-up; alpha = 0.05, power = 0.67, HR 0.5; intention-to-treat.



2000 design …
+
TRM 10%.

Primary endpoint: Event Free Survival = OS without persistent major organ failure (heart, lung, kidney)

[c] Lung (respiratory) failure was defined by the study protocol as resting arterial oxygen tension (PaO2) < 8 kPa (< 60 mmHg) and/or resting arterial carbon dioxide tension (PaCO2) > 6.7 kPa (> 50 mmHg) without oxygen supply.

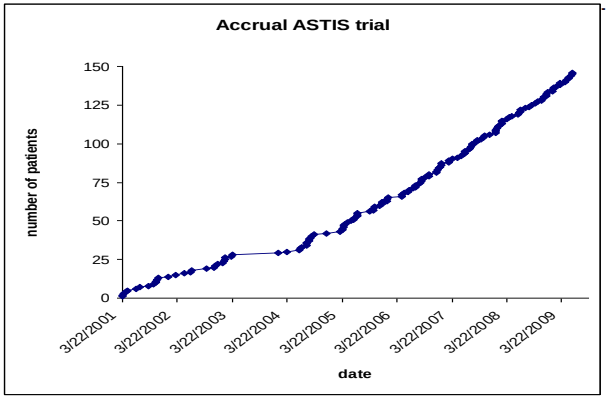
[d] Heart failure was defined as left ventricular ejection fraction < 30% by multiple gated acquisition scan (MUGA) or cardiac echo.

[e] Renal failure was defined as need for renal replacement therapy.

Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial

Original Investigation Research

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368



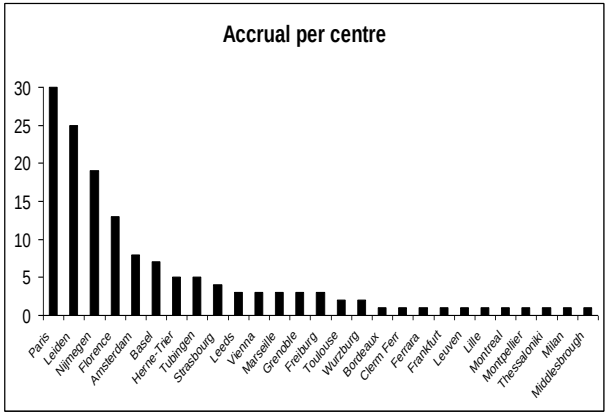
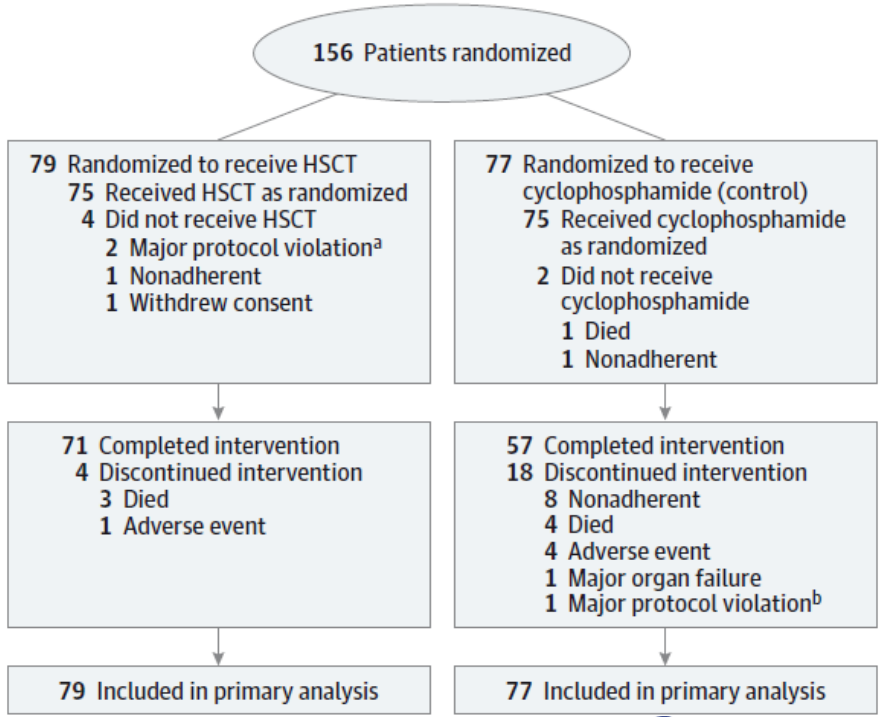


Figure 1. Flow of ASTIS (Autologous Stem Cell Transplantation International Scleroderma) Trial



France: 49; Netherlands: 54 Allemagne: 20; Italie: 16

Suisse 7, GB: 5, Austriche:3, Belgique 1, Can1 1Grece: 1

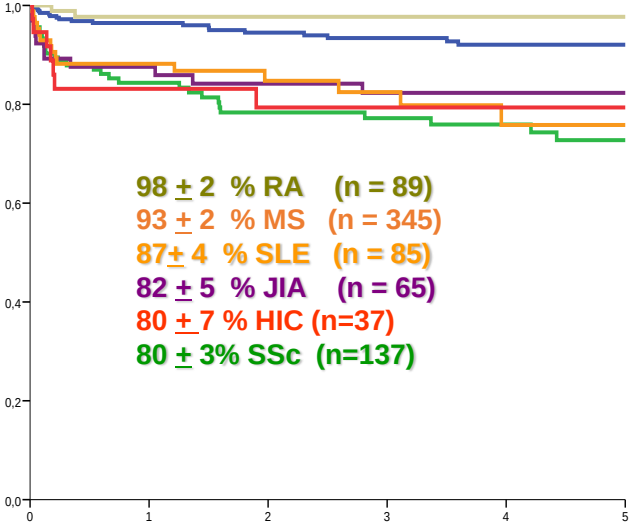
EBMT DRCD- PHRC AP-HP

Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases

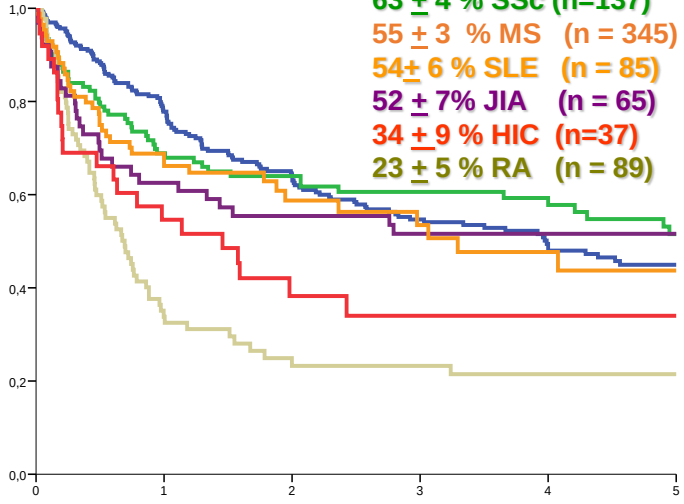
Dominique Farge,[1] Myriam Labopin,[2] Alan Tyndall,[3] Athanasios Fassas,[4] Gian Luigi Mancardi,[5] Jaap Van Laar,[6] Jian Ouyang,[7] Tomas Kozak,[8] John Moore,[9] Ina Kötter,[10] Virginie Chesnel,[11] Alberto Marmont,[12] Alois Gratwohl,[13] and Riccardo Saccardi[14]

haematologica | 2009; 95(2)

Overall Survival 3 yrs (n= 900)



PFS 3 yrs (n=900)



1. CENTRE EFFECT ON TRM, OS, PFS :
According to activity center (n ≥ 13);

100 D TRM for SSC : 6 %

in 2018: 520 SSc in the EBMT registry

100-day transplant-related mortality*	P	HR	95.0% IC
Centers' experience	0.003	0.32	0.16-0.69
Diagnosis	0.03		
Multiple sclerosis		1.78	0.21-14.8
Systemic sclerosis		4.45	0.56-35.4

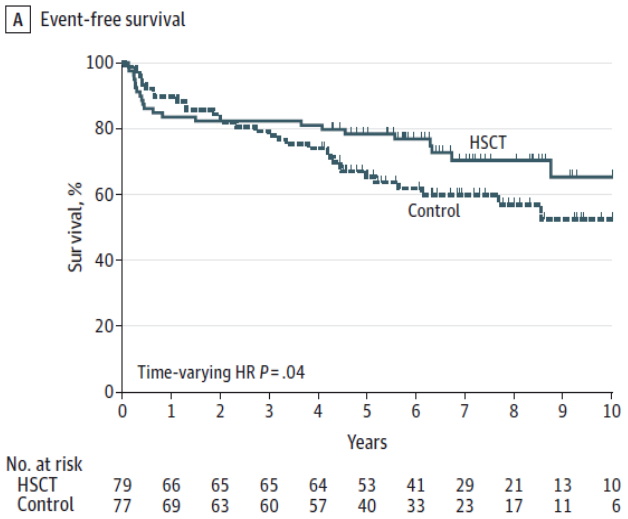
Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial

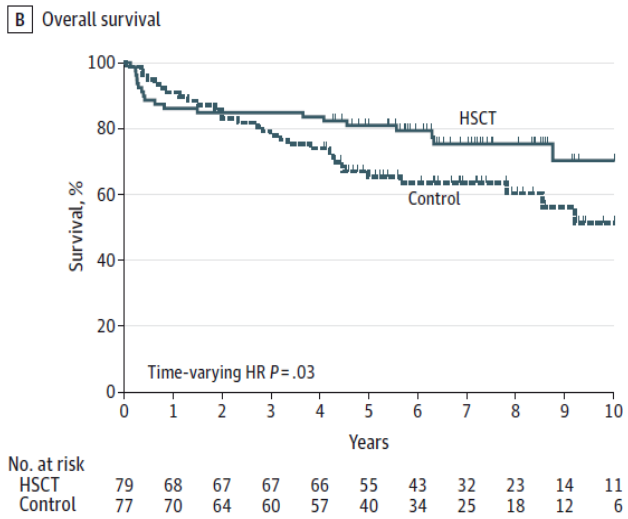
Original Investigation Research

Van Laar JVL and Farge D et al

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

Figure 2. Event-Free and Overall Survival During 10-Year Follow-up





Exclusion criteria : ECG + TTE, No RHC
mPHT > 50 mmHg +++
DLCO < 40%
LVEF < 45%

8 TRM during 1st yr: at least 4 LV (2 ischemia , 2 HF)

	HSCT Group (n = 79)	Control Group (n = 77)	
Adverse event of grade 3-4			
Respiratory	15 (19.0)	6 (7.8)	.06
Cardiovascular	13 (16.5)	8 (10.4)	.35

2. Patients selection

Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

Table Baseline Characteristic of Study Patients

Characteristic	All Patients (N=156)	AHSCT n= 79	Control n = 77
Age - yr	43.8 (11.3)		
Female sex – no. (%)	92 (59.0)		
Disease Duration - yr	1.4 (1.3)		
Major organ involvement – no. (%)			
Lung	135 (86.5)		
Kidney	5 (3.2)		
Heart	13 (8.3)		
None	16 (10.3)		
Current or past smoker– no. (%)	84 (53.8)		
Pre-trial use of cyclophosphamide – no.	34 (21.8)		
Weight (kg)	68.6 (14.4)		
BMI	23.8 (4.1)		
Modified Rodnan skin score (mRSS)	25.3 (8.0)		
Creatinine clearance (mL/min)	76.7 (25.9)		
LVEF by echo	64.9 (8.5)		
VC (% of predicted)	81.4 (18.4)		
DLCO (% of predicted)	58.5 (14.1)		
HAQ score	1.35 (0.8)		
Modified Rodnan skin score, mean (SD)[d]	25.3 (8.0)	24.8 (8.1)	25.8 (7.9)
Creatinine clearance, mean (SD), mL/min[e]	76.7 (25.9)	76.8 (26.1)	76.5 (26.0)
Cardiac			
Abnormal electrocardiogram[f]	24 (16.0)	10 (13.2) [n = 76]	14 (18.9) [n = 74]
Pericardial effusion	12 (7.8)[g]	4 (5.1) [n = 78]	8 (10.5) [n = 76]
LVEF (%) by cardiac echocardiography, mean (SD)	65.6 (7.6)	65.6 (7.5) [n = 70]	65.7 (7.8) [n = 67]
Lung			
Abnormal thoracic computed tomography[h]	125 (83.3)	66 (86.8) [n = 76]	59 (79.7) [n = 74]
Forced vital capacity, mean (SD), % predicted	81.4 (18.4)	81.7 (19.3)	81.1 (17.6)
Total lung capacity, mean (SD). % predicted	80.7 (16.6)	81.0 (17.1) [n = 75]	80.5 (16.2) [n = 75]
Residual volume, mean (SD), % predicted	90.1 (30.3)	90.4 (30.1) [n = 71]	89.9 (30.6) [n = 71]
DLCO mean (SD), % predicted	58.5 (14.1)	59.3 (14.3) [n = 79]	57.7 (14.0) [n = 76]
Pulmonary arterial hypertension[i]	10 (6.6)	4 (5.2) [n = 77]	6 (8.1) [n = 74]
HAQ-DI, mean (SD)[j]	1.35 (0.80)	1.25 (0.74) [n = 68]	1.44 (0.84) [n = 73]
SF-36, mean (SD)[k]		[n = 59]	[n = 66]
Physical component	32.2 (10.0)	32.2 (10.4)	32.2 (9.6)
Mental component	42.0 (11.4)	41.2 (10.7)	42.6 (12.0)
EQ-5D, mean (SD)[l]		[n = 65]	[n = 73]
Index-based utility score	0.47 (0.32)	0.46 (0.32)	0.47 (0.32)
VAS score	51.9 (21.5)	53.4 (22.1)	50.7 (21.1)

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

Van Laar JVL and Farge D et al

Events (deaths and major organ failure) with causes ascertained by independent-data monitoring committee

ASTIS trial December 2012 JvL*-DF*-AT
(May 2012 data cut-off)

19 Transplant arm

- Died n=16
  - Procedure-related n=8
  - *Disease progression n=5*
  - *Major organ failure n=1*
  - Stroke n=1
  - Sepsis n=1
- Major organ failure n=3

27 Control arm

- Died n=26
  - *Disease progression n=15*
  - cancer n=4
  - *Major organ failure n=3*
  - Sudden death n=3
  - Suicide n=1
- Major organ failure n=1

Causes of TRM Heart failure (n=3) Hemodynamic shock multi-organ failure (n =1) ARDS (n = 2) Multiple organ failure (n = 1) Pulmonary odema (n = 1)

Type of Major Organ Failure[a]	Transplant Group (n=3)	Control Group (n=8)[b]
Lung[c]	1 (33.3)	3 (37.5)
Heart[d]	0	2 (25.0)
Renal[e]	2 (66.7)	3 (37.5)

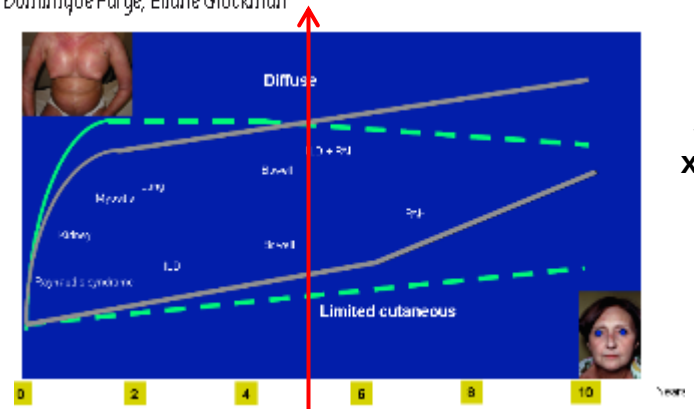
7 died subequently

Cytokines release 33% (n = 21)

Autologous HSCT in systemic sclerosis: a step forward

www.thelancet.com Published online July 20, 2011 DOI:10.1016/S0140-6736(11)61100-8

*Dominique Farge, Eliane Gluckman

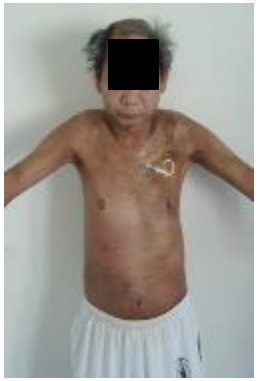


HSCT ***MSC***

@

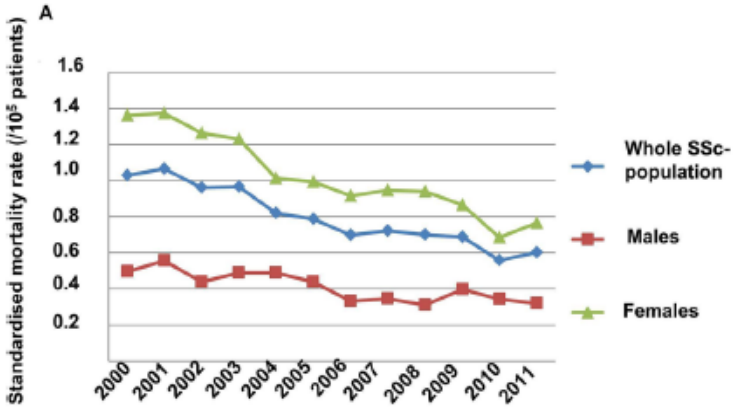
Prevalence 7–500 / Million

x 1.2 -1.8 femmes noires



1996--2018

Standard Mortality Rate
x 3.5 / general population



Elhai et al Ann Rheum Dis 2017

SSc 5 years survival

No of risk factors	Total no of patients	No of patients deceased	Mortality (%)	Mortality (%) Bryan *et al*[6]
0	509	12	2.2	7.1
1	349	45	12.9	22.8
2	168	55	32.7	54.8
3	23	7	30.4	100

The table presents the number of risk factors according to the prognostic model of 5-year survival for newly diagnosed systemic sclerosis.[6] The number of patients and mortality in the current study are compared with the mortality in the original study by Bryan *et al*.[6]

Fransen J et al Ann Rheum Dis 2012

Left Ventricle Replacement Fibrosis Detected by CMR Associated With Cardiovascular Events in Systemic Sclerosis Patients

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Gilles Soulat, MD
Dominique Farge, MD, PhD

JACC VOL. 71, NO. 6, 2018
FEBRUARY 13, 2018:700-9

B

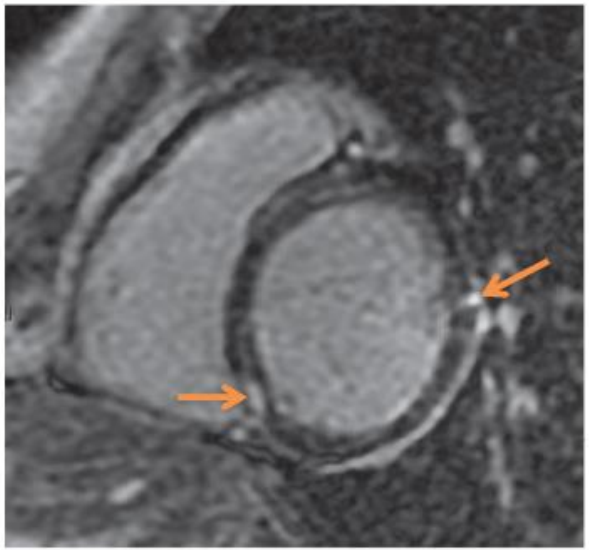
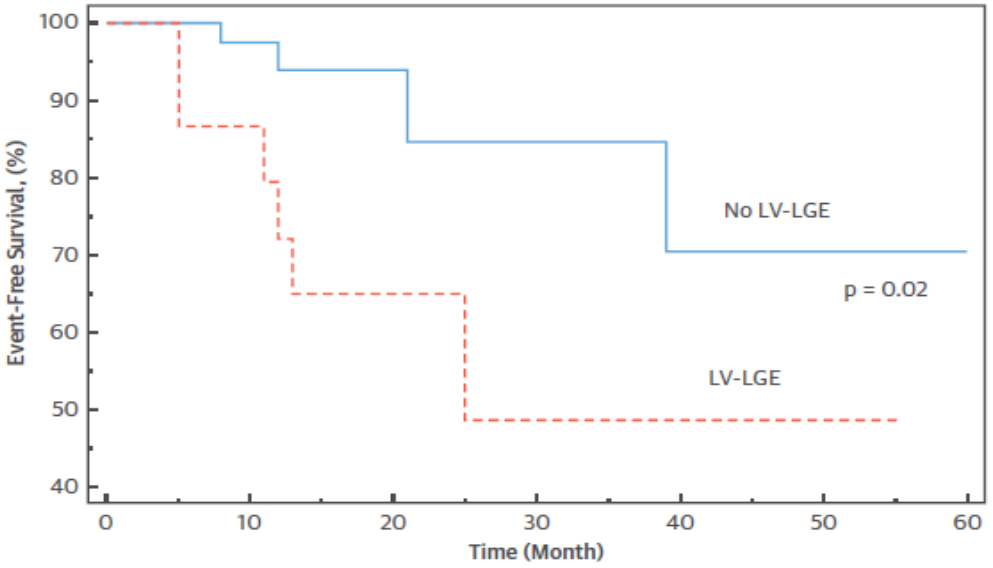


FIGURE 1 Kaplan-Meier Survival Curves for LV LGE or No-LV-LGE

A



Number at risk						
Group: No LV-LGE						
41	28	10	8	5	1	0
Group: LV-LGE						
15	12	4	3	2	2	0

(A) Kaplan-Meier survival curves are shown of the time to event according to the presence (LV-LGE) or absence (No-LV-LGE) of left ventricular late gadolinium enhancement in CMR. **(B)** One case illustrates CMR presence of LV-LGE with a nodular pattern of focal enhancement at 2 different locations **(arrows)**. CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricle.

2. CONTRA- INDICATIONS or EXCLUSION to AHSCT

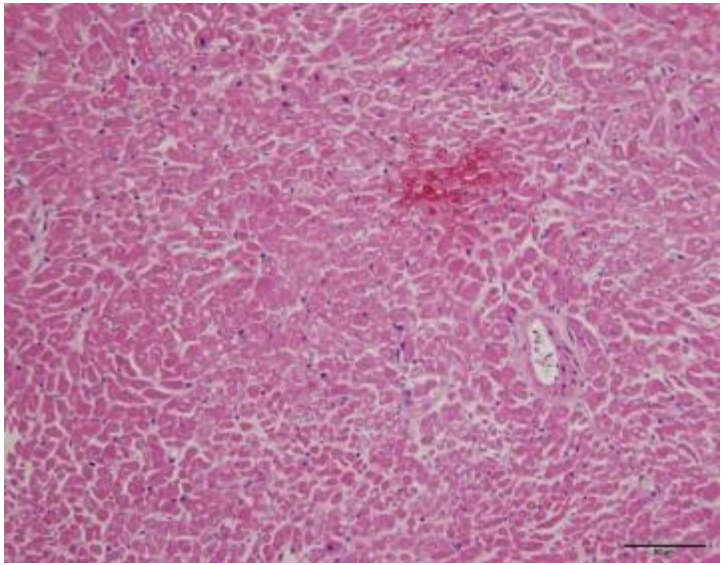
Age	**> 65 years**
Pregnancy	Pregnancy or unadequate contraception throughout investigation
Psychiatric	Psychiatric disease including alcohol or drug abuse
Consent	Inability to provide informed consent for treatment
Liver function	Liver function test abnormalities (i.e. 2-fold transaminases or bilirubin, cirrhosis)
Neoplasms	Concurrent neoplasms or myelodysplasia or haematological disorders
Infection	Active acute or chronic infection, including HIV, HTLV-1,2, hepatitis B and C, active cancer or major side effects of previous cancer treatment
Heart	LVEF <45% or impaired RV or LV function, significant atherosclerotic or valvular heart disease, pericardial effusion with haemodynamic consequences atrial or ventricular arrhythmia or 2nd or 3rd degree heart block.
LUNG	Any significant SSc or non-SSc related respiratory disease with respiratory failure (PaO_2 <8.0 kPa), interstitial lung disease with FVC <65% or **DLCO-SB < 65 %** extensive disease on HRCT, mean PAP≥25mmHg **Smoking**
Renal	Any definite SSc renal crisis in the previous 6 months or non-scleroderma related renal disease defined as creatinine clearance<40 ml/min

Snowden J, et al. BMT 2012 ; Farge and Burt et al BMT 2017.

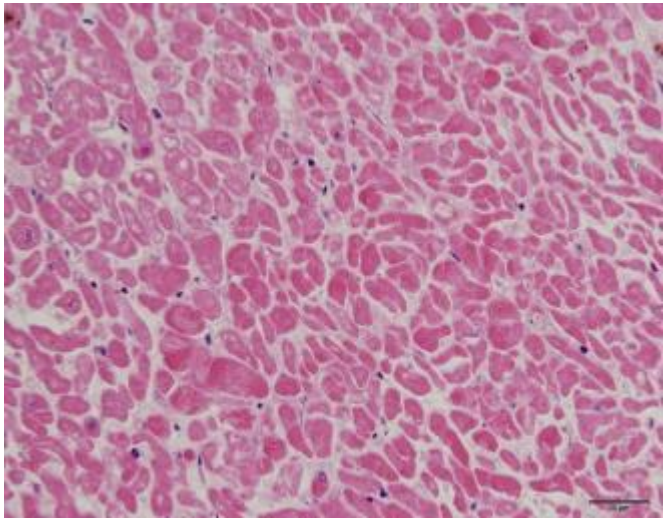
ACUTE CYCLO CARDIOTOXICITY

Martin et al BMT 2017

within 3 wks after iv CYCLO toxic endothelial damage



diffuse interstitial oedema
no evidence of fibrosis nor inflammatory infiltrate (x 20)



Diffuse ischemic myocardial necrosis:
nuclear extravasation or pycnosis, hyperstaining by eosin.
Intracellular oedema and diffuse interstitial oedema (X40).

THE REAL RISK

Cardiac involvement and treatment-related mortality after non-myeloablative haemopoietic stem-cell transplantation with unselected autologous peripheral blood for patients with systemic sclerosis: a retrospective analysis

www.thelancet.com Published online January 28, 2013

N = 90 pts : 5 %TRM

Richard K Burt, Maria Carolina Oliveira, Sanjiv J Shah, Daniela A Moraes, Belinda Simoes, Mihai Gheorghiade, James Schroeder, Eric Ruderman, Dominique Farge, Z Jessie Chai, Zora Marjanovic, Sandeep Jain, Amy Morgan, Francesca Milanetti, Xiaoqiang Han, Barko Jovanovic, Irene B Helenowski, Julio Voltarelli*

1 The main outcome was treatment-related mortality

2 thickness by modified Rodnan skin score and pulmonary function by forced vital capacity, total lung capacity, and diffusing capacity of carbon monoxide (DLCO; percentage predicted and corrected for haemoglobin). We administered quality of life questionnaires (short form [SF]-36) for the last 30 consecutive patients from

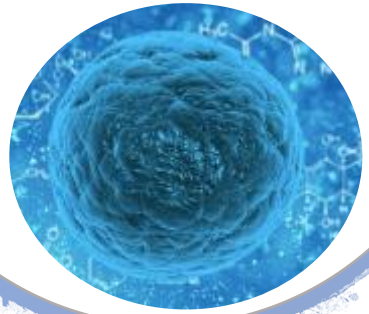
3 one site (Northwestern University). We defined relapse as any of the following criteria: increase from best improvement of skin score by 25% or decline in forced vital capacity by 10%, renal crisis, start of total parenteral nutrition, or restarting of immune suppressive or modulating medication.

	Normal echocardiogram or electrocardiograph or female sex	Abnormal echocardiogram or electrocardiograph or male sex	p value*
DLCO			
Group: echocardiogram	Normal 71·3% (3·1)	Abnormal 56·7% (3·8)†	0·0045
Group: electrocardiograph	Normal 73·3% (4·6)	Abnormal 62·0% (3·0)†	0·045
Group: sex	Female 66·3% (2·8)	Male 64·5% (4·9)	0·75
FVC			
Group: echocardiogram	Normal 70·8% (3·2)	Abnormal 68·4% (2·4)	0·58
Group: electrocardiograph	Normal 73·6% (4·6)	Abnormal 68·2% (2·1)	0·28
Group: sex	Female 66·1% (2·5)	Male 66·3% (3·1)	0·95
Total lung capacity			
Group: echocardiogram	Normal 80·3% (3·4)	Abnormal 78·8% (2·3)	0·70
Group: electrocardiogram	Normal 81·9% (4·4)	Abnormal 78·7% (2·1)	0·51
Group: sex	Female 75·8% (2·4)	Male 75·2% (3·0)	0·80
mRSS			
Group: echocardiogram	Normal 16·1 (1·7)	Abnormal 18·2 (1·3)	0·33
Group: electrocardiograph	Normal 16·1 (2·4)	Abnormal 17·8 (1·1)	0·51
Group: sex	Female 17·0 (1·4)	Male 16·4 (2·1)	0·77

Response to treatment: 25% ↑ mRSS and/or≥10% ↑ DLCO or FVC at month 12

SSC PATIENT selection :

EKG, cardiac echo with TAPSE, 24h Holter, MRI , right heart catheter with fluid challenge



AHSCT in SSc?

Questions from the (Canadian) clinician

- If there are C-I, why not give the patient the choice? **Sure not**
- SRC as an inclusion criteria - that does not make sense to me? **Why not**
- TBI - as a clinician, radiation scares me a lot! **Me too**
- ACEi prophylaxis - really? **Yes indeed**
- Molecular profiling - what about simpler biomarkers like serologies? **Little evidence**

Marie Hudson, MD MPH FRCPC
Jewish General Hospital
Lady Davis Institute

McGill

After careful patients selection and center referal: beyond ASTIS
Which could be the best trial design in a rare disease ?

A Can AHSCT for SSc be safer with improved conditioning regimen ?

Fludarabine ? Lower dose Cytoxan ?

B How to improve patients follow up ?

Patient clinical, infectious and biological monitoring:
Rodnan, SHAQ, CVF + Immune monitoring

C Which response criteria : Non responders and Relapsing patients

D How to predict the clinical response ? Response criteria: definition

E Maintenance therapy after AHSCT

eTable 6. Viral Infections and Reactivations After Randomization

Viral infection/reactivation	Transplant Group Patients, No/Total Patients, No (%)		Control Group Patients, No/Total Patients, No (%)
Cytomegalovirus (CMV)			
Primary infection[a]	2/40 (5.0)		0
Recurrent CMV infection[b]	7/37 (18.7)		0
Symptomatic CMV infection[c]	3/7 (42.9)		0
CMV disease	0		0
Epstein-Barr virus (EBV)			
Primary infection	0		0
Reactivation[d]	6/48 (12.5)		0
EBV-related PTLD[e]	2/6 (33.3)		0
Herpes simplex virus (HSV)			
Primary infection[f]	2/29 (6.9)		1/35 (2.9)
Reactivation[g]	9/41 (22.0)		0
CMV/ HSV co-infection	3/79 (3.8)		0
Varicella zoster virus (VZV)			
Primary infection	0		0
Reactivation[h]	3/50 (6.0)		0
Hepatitis B virus (HBV)			
Chronic infection[i]	1/1 (100.0)		0

Twenty-two and one patients in the HSCT and control groups respectively had at least one viral infection episode after randomization (*P*<.001). Some patients experienced more than one viral infection episode.

[a] Primary CMV infection was defined as detection of CMV in a previously seronegative patient. One patient had a CMV/HSV co-infection and was treated with aciclovir.

[b] Recurrent CMV infection was defined as detection of CMV in a previously seropositive patient. Two patients were treated with ganciclovir, one patient with ganciclovir and valganciclovir, and one patient with valganciclovir.

[c] Three patients had symptomatic CMV infection: one had diarrhea with a normal colonoscopy, one patient had pulmonary symptoms, and one patient had CMV-related pancytopenia and was treated with ganciclovir and, because of lack of efficacy, subsequently with foscarnet.

[d] One patient with asymptomatic EBV reactivation was treated with rituximab.

[e] Two patients presented with EBV lymphoma; one patient was successfully treated with rituximab, one patient died (treatment-related mortality).

[f] In the transplant group, 1 patient was treated with aciclovir and 1 patient with valaciclovir.

[g] Six patients were treated with aciclovir, and one patient with aciclovir and valaciclovir.

[h] Two patients were treated with aciclovir.

[i] Patient was treated with entecavir.

Table 2. Treatment Responses in Clinical Outcome Variables, Change in the Area Under the Time Response Curve From Baseline to 2 Years' Follow-up

Variable	AUC, Mean (SD)		Difference (95% CI)	*P* Value
	HSCT Group (n = 67)[a]	Control Group (n = 64)[a]		
Weight, kg	-0.7 (9.5)	-0.8 (9.6)	-0.2 (-3.5 to 3.1)	.91
Modified Rodnan skin score	-19.9 (10.2)	-8.8 (12.0)	11.1 (7.3 to 15.0)	<.001
Creatinine clearance, mL/min[b]	-12.1 (29.7)	-1.2 (24.1)	10.9 (1.5 to 20.3)	.02
LVEF, % by cardiac echocardiography	-2.2 (14.7)	-1.9 (13.8)	0.3 (-4.7 to 5.2)	.91
Forced vital capacity, % predicted	6.3 (18.3)	-2.8 (17.2)	-9.1 (-14.7 to -2.5)	.004
Total lung capacity, % predicted	5.1 (17.5)	-1.3 (13.9)	-6.4 (-11.9 to -0.9)	.02
Residual volume, % predicted	-4.8 (33.7)	-2.1 (26.9)	2.7 (-7.9 to 13.2)	.62
DLCO, % predicted	-4.7 (13.7)	-4.1 (17.6)	0.6 (-4.9 to 6.0)	.84
HAQ-DI	-0.58 (1.14)	-0.19 (0.79)	0.39 (0.51 to 0.73)	.02
SF-36 score				
Physical component	10.1 (15.8)	4.0 (11.2)	-6.1 (-10.9 to -1.4)	.01
Mental component	3.1 (16.0)	3.4 (17.1)	0.3 (-5.41 to 6.07)	.91
EQ-5D				
Index-based utility score	0.31 (0.50)	0.03 (0.44)	-0.29 (-0.45 to -0.12)	<.001
VAS score	16.9 (44.5)	10.2 (39.7)	-6.7 (-21.33 to 7.87)	.36

Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis

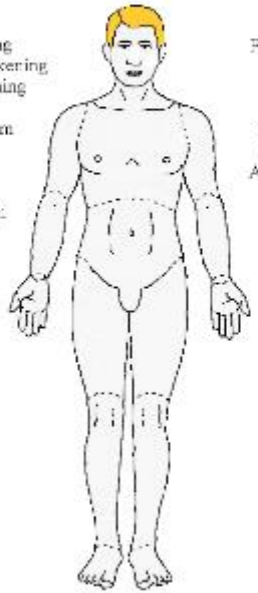
J Scleroderma Relat Disord 2017 ; 2(1): 11–18.

Dinesh Khanna[1], Daniel E. Furst[2], Philip J. Clements[2], Yannick Allanore[3], Murray Baron[4], Lazlo Czirjak[5], Oliver Distler[6], Ivan Foeldvari[7], Masataka Kuwana[8], Marco Matucci-Cerinic[9], Maureen Mayes[10], Thomas Medsger Jr[11], Peter A. Merkel[12], Janet E. Pope[13], James R. Seibold[14], Virginia Steen[15], Wendy Stevens[16], and Christopher P. Denton[17] on behalf of the Scleroderma Clinical Trials Consortium and the World Scleroderma Foundation

Name: Datum:

MODIFIED RODNAN SKIN SCORE

0 Uninvolved
1 Mild thickening
2 Moderate thickening
3 Severe thickening



Face ☐
Upper arm ☐ Upper arm ☐
Anterior chest ☐
Abdomen ☐
Forearm ☐ Forearm ☐
Hand ☐ Hand ☐
Fingers ☐ Fingers ☐
Thigh ☐ Thigh ☐
Leg ☐ Leg ☐
Foot ☐ Foot ☐

Total Skin Score .....

15 % variability between 2 examinators
+ 25% to be significant

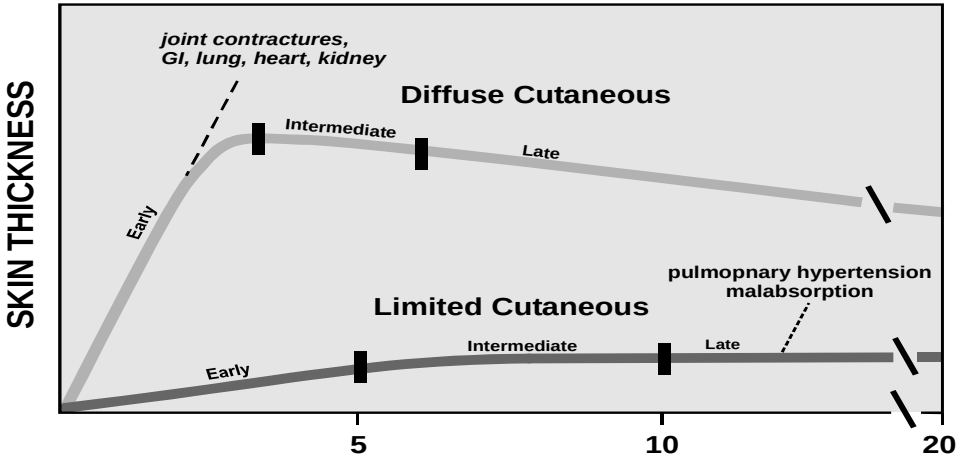
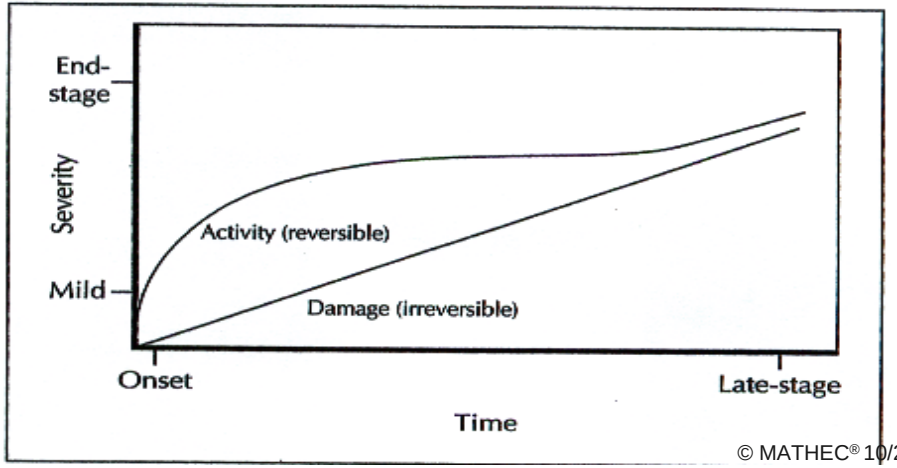
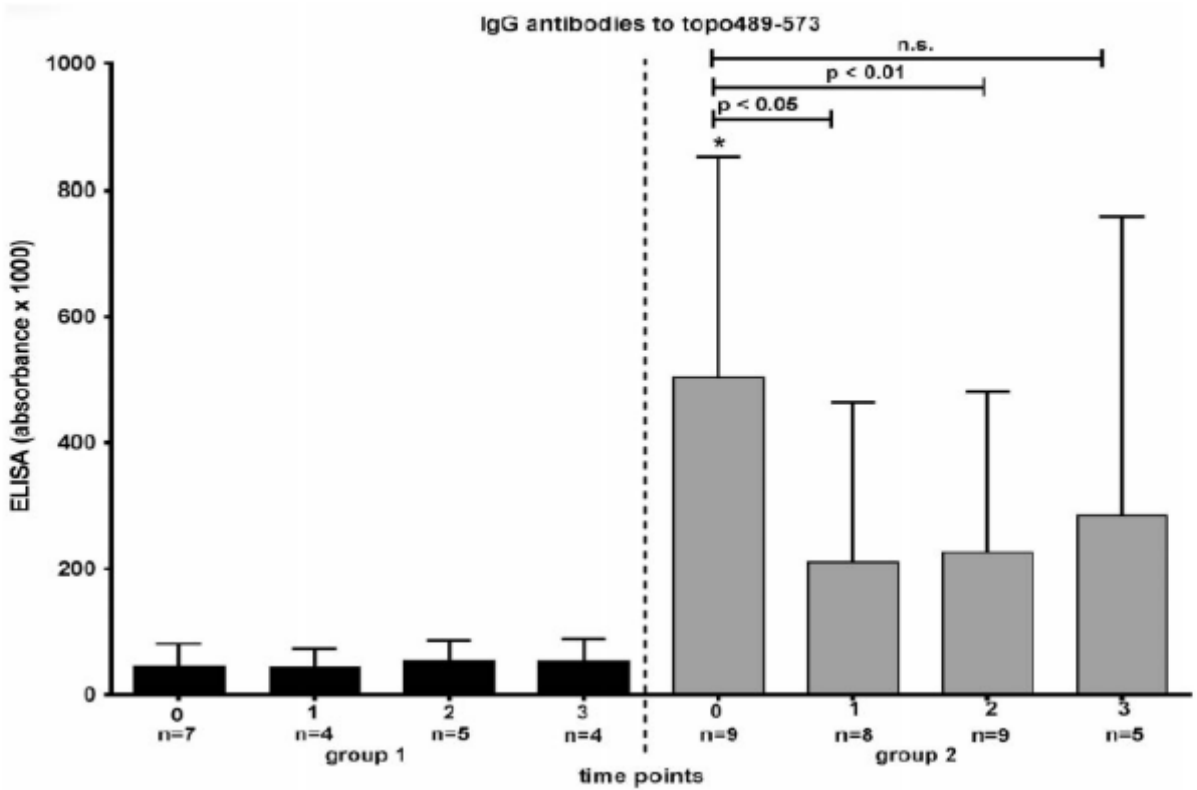


Figure 1. Schematic relation between disease damage and disease activity in systemic sclerosis



Analysis of anti topoisomerase I antibodies in patients with systemic sclerosis before and after autologous stem cell transplantation

FIG. 2 Anti-topo I reactivity against the immunodominant epitope 489-573 in SSc patients before and after autologous stem cell transplantation

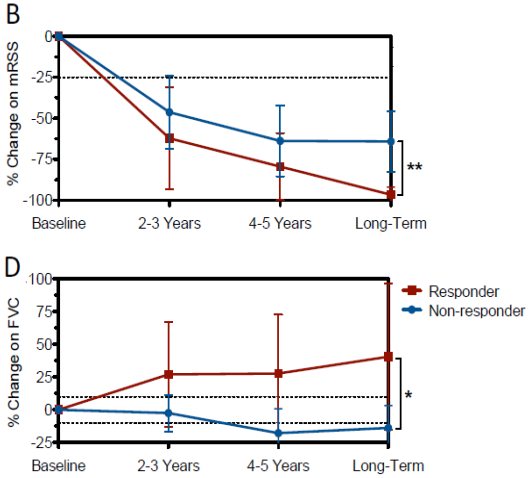


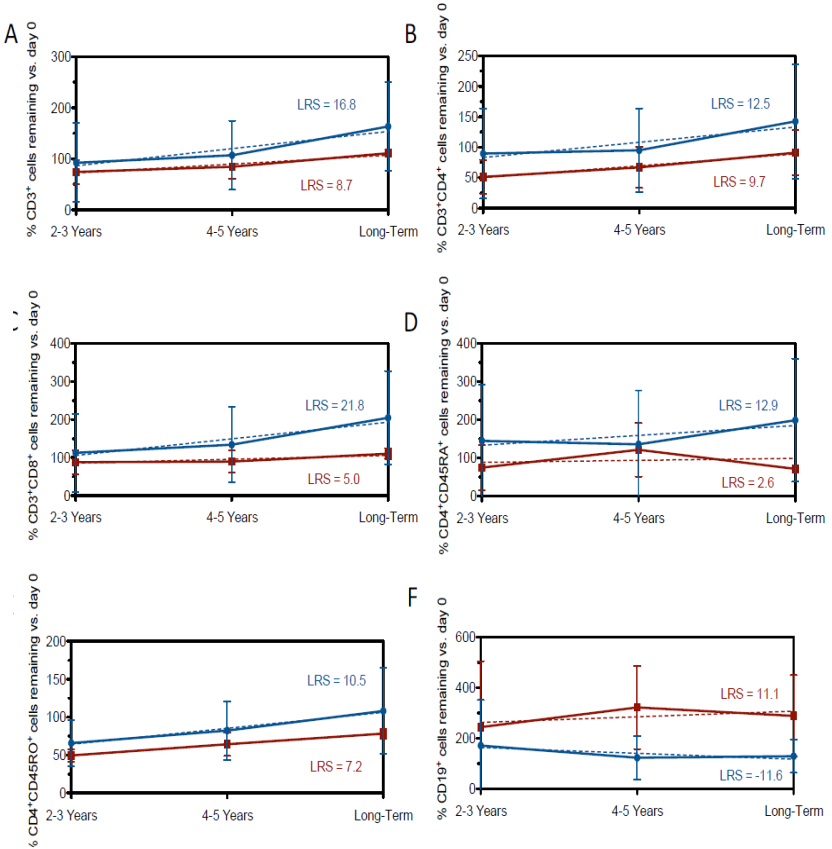
Jorg Henes, RHEUMATOLOGY, 2016

Long-term immune reconstitution and T-cell repertoire analysis after autologous HSCT in systemic sclerosis patients

Farge et al. Journal of Hematology & Oncology (2017) 10:21

Long-term mRSS fall > 25%
more pronounced in pts improving
FVC% > 10% (*P*=0.026





Pretransplant B cell clonal expansion
+ faster T-cells IR after aHSCT in non-responders
/relapsing

Table 3 Anti-scl-70 autoantibodies

	Group A patients					Group B patients				
	1	2	3	4	5	1	2	3	4	5
Anti-Scl-70 antibodies, U/ml										
Baseline	120	+[a]	0	10.2	+[a]	0	+[a]	39.1	130	21.3
2–3 years	32.9	0	0	0	390	0	240	31.1	106.5	0
4–5 years	11.6	0	0	0	257	0	352	15.9	+[a]	0
Long term	0	0[b]	0[b]	0	>8[b]	0	3.8[b]	>8[b]	250	0

Anti-Scl-70 antibodies were measured at pre-transplant period (baseline) and sequentially during follow-up by enzyme-linked immunosorbent assay as described in methods section. Quantified results are expressed in arbitrary units/ml as previously published ([8])
[a]Positive for Anti-Scl-70 antibodies
[b]Anti-Scl-70 antibodies levels measured by BioPlex ANA Screen

Farge *et al. Journal of Hematology & Oncology* (2017) 10:21
DOI 10.1186/s13045-016-0388-5

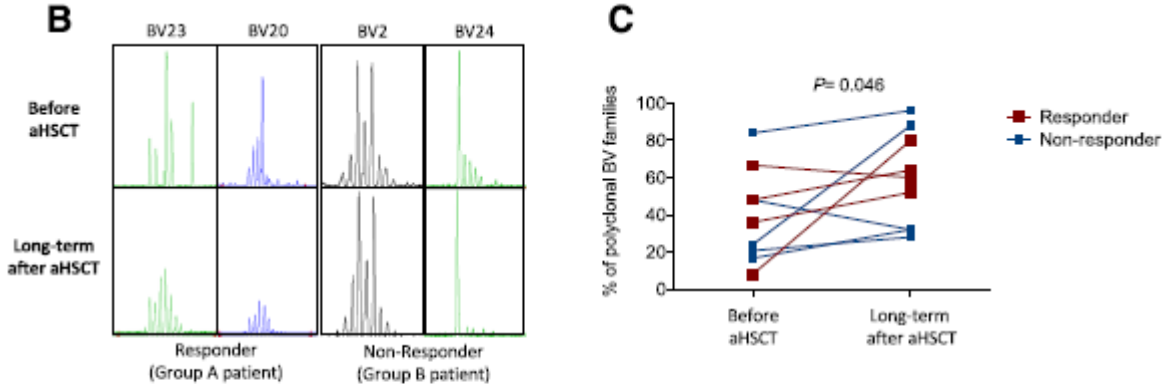


Fig. 3 TCR-Vβ family expression and T cell receptor β-chain spectratyping before and at long-term after aHSCT. **a** Quantification of each TCR-Vβ family at baseline (*white bars*) and at long-term (*dark bars*) after aHSCT in 10 dcSSc patients. Data are presented as mean ± SD. There are no differences between the clinical groups. **b** TCR-Vβ chain third complementarity-determining region size distribution profile of selected families at baseline (pre, *upper level*) and at long-term time point (*lower level*) for representative dcSSc patients who underwent autologous hematopoietic stem cell transplantation. *Left*: Polyclonal distribution achievement at long-term time point post-HSCT from a skewed and disturbed repertoire at baseline (patient 3, group A, responder). *Right*: Sustained disturbed distribution at long-term time point post-HSCT from a previously skewed profile at baseline (patient 1, group B, non-responders or relapse or necessitating immunosuppression). **c** T cell repertoire diversity as measured by the percentage of polyclonal TCR-Vβ families in all 10 dcSSc patients at baseline and at long-term follow-up (at least 6 years) after aHSCT

SSc Patients		
AHSCT		**Non-AHSCT**
31		**16**
University of Ribeirao Preto Medical School, Brazil (2010 to 2015)		St-Louis, Paris (ASTIS controls or contra indication for AHSCT)
Responders (n=25)	**Non-responders (n=6)** Relapsing: At least 1of ↗mRSS > 25% from best improvement ↘CVF >10% Renal crisis Start of total parenteral nutrition Restarting mmunosupressor treatment * Burt, Lancet, 2013	

METHODS

T cells

1. Newly-generated Naive T-cells

2. T-cell clonotypes

3. T-Reg Cells

B cells

1. Newly-generated Naive B-cells

2. B-cells differenciation analysis
   : from naive to memory B-cells

3. Breg cells

Coelho L et Oliveira et al Blood advances 2017

Conclusions

	SSc Pathophysiology	Non-AHSCT patients (16)	AHSCT patients (31)	
			Responders (25)	Relapsing (6)
LT	↘ thymopoiesis	T-cell stable (nb)	Rebound of LT production → naive T-cell output	
	↘ TCR diversity		TCR diversity +++	TCR diversity +
	↘ **Treg** (Nb, function)		↗ Nbr Treg	
			↗ modulation markers of Treg	No change of modulation markers of Treg
LB	B-cell hyperactivation	B-cell stable (Nb)	↗ B-cell through naive B-cell output	
	↘ **Breg** (Nb)		↗ **Breg** (Nbr) and ↗IL-10	
	↘IL-10		↗ **Breg**	↗ **Breg**

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eTable 4. Immunosuppressive Drugs Used Between 12 and 24 Months

Drug Name	Transplant Group (n=67)		Control Group (n=64)
Glucocorticoids	12 (17.9)		12 (18.7)
Mycophenolate	4 (6.0)		10 (15.6)
Azathioprine	0		9 (14.1)
Cyclophosphamide[a]	0		3 (4.7)
Methotrexate	0		2 (3.1)
Infliximab	0		1 (1.6)
Docetaxel[b]	0		1 (1.6)
Adriamycine[c]	0		1 (1.6)
Rabbit anti-thymocyte globulin[d]	0		1 (1.6)

Values are No (%) of patients.
Sixty-seven patients in the transplant group and 64 patients in the control group were still alive at two years after randomization and were included in the analysis. Fifteen and 28 patients in the HSCT and control groups respectively received at least one immunosuppressive drug between 12 and 24 months (*P*=.02). Some patients received more than one immunosuppressive drug during this period.
[a] Cyclophosphamide received after the completion (or withdrawal) of the trial treatment. One patient in the control group received cyclophosphamide as part of the rescue transplant treatment. Another patient in the control group received cyclophosphamide as part of a chemotherapy regimen for breast cancer.
[b] Docetaxel received as part of a chemotherapy regimen for breast cancer.
[c] Adriamycine received as part of a chemotherapy regimen for breast cancer.
[d] Rabbit anti-thymocyte globulin received as part of rescue transplant treatment.

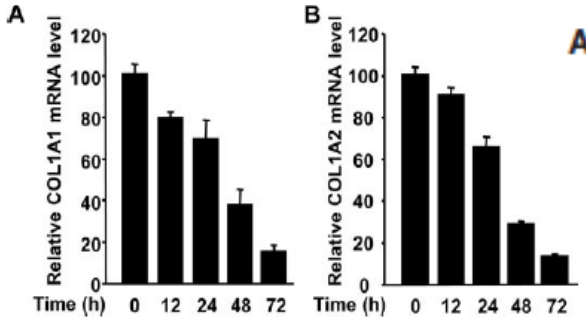
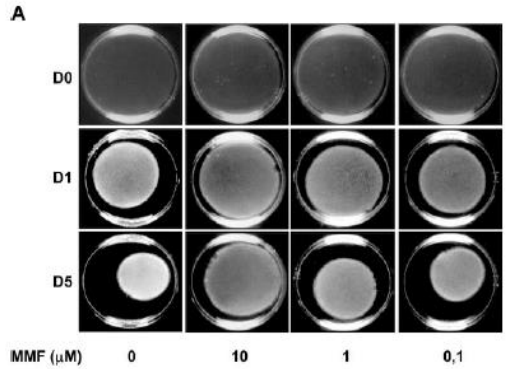


Fig. 2. MMF decreases COL1A1 and COL1A2 mRNA levels. Confluent fibroblast cultures were treated with MMF (10 μM) for 12, 24, 48, or 72 h, following which total RNA was extracted, and *COL1A1* (A) and *COL1A2* (B) mRNA steady-state levels were determined by quantitative RT-PCR.

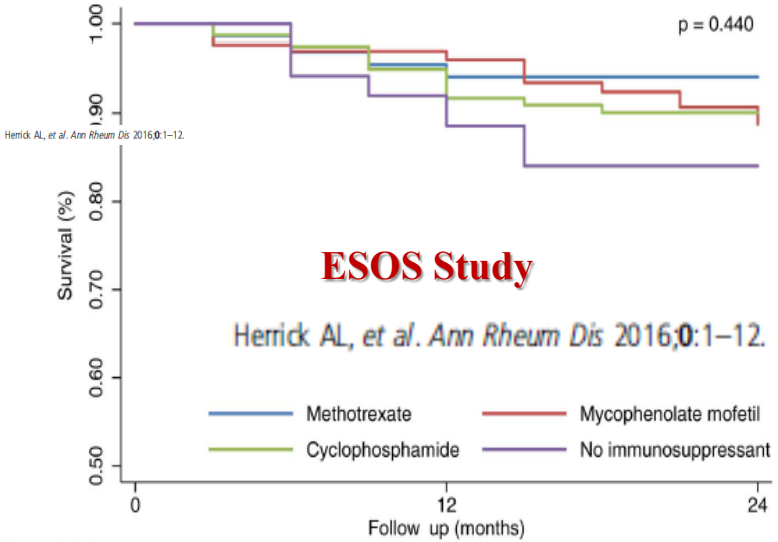
Antifibrotic Activity of Mycophenolate Mofetyl

Nina Roos, Nicolas Poulalhon, Dominique Farge, Isabelle Madelaine, Alain Mauviel, and Franck Verrecchia

JPET 321:583–589, 2007



WHICH TREATMENT FOR SSc ?



ESOS Study

Herrick AL, *et al. Ann Rheum Dis* 2016;**0**:1–12.

Number at risk

Methotrexate	65	54	45
Mycophenolate mofetil	118	108	82
Cyclophosphamide	87	75	55
No immunosuppressant	56	50	32

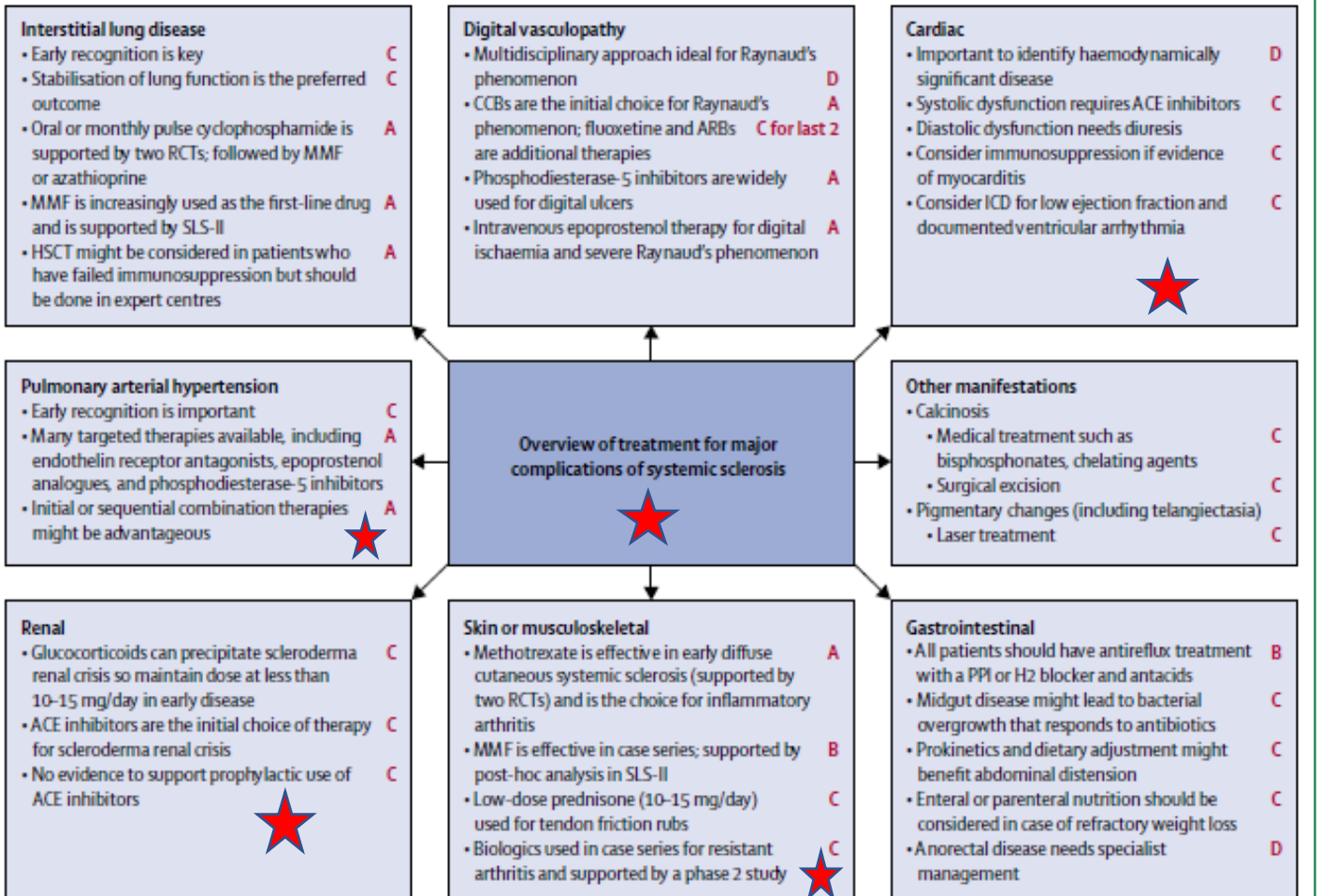
Systemic sclerosis

www.thelancet.com Published online April 13, 2017

Christopher P Denton, Dinesh Khanna

2014 update of the 2007 EULAR endorsed recommendations

2018 +++



Maladies Autoimmunes
Thérapies Cellulaires

MATHEC
Maladies Auto Immunes & Thérapie Cellulaire

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St Louis (UH 04)
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Groupe Hospitalier Universitaire SAINT-LOUIS LARIBOISIERE FERNAND-WIDAL

NTIC : procédures communes, EBMT, Registre

Traitement SSc par MSC allogéniques ? 2011 phase I-II trial
Traitement LED par MSC Cordon ? Prix Fondation Rein