STEM CELL THERAPY FOR AUTOIMMUNE AND AUTOINFLAMMATORY DISEASES

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www.mathec.com

Cellules Souches Hématopoiétiques : Moelle Osseuse, Périphérie, Cordon

REINDUCTION de la TOLERANCE

Greffe Moelle ..... **CSM**

Cyclophosphamide *po*, iv
Biothérapies

CORTICOIDES

Serum Antilymphocytaire **CYCLOSPORINE A**

1960 | 1970 | 1980 | 1990 | 1995 | 2000 | 2005 | 2010 | 2020

Formes sévères or rapidement évolutives de MAI :

Sclérodermie systémique[1]

Survie 5 ans 30 % 40 %

Lupus Systémique[2]

Survie 10 ans /IR 70/50 % 90/35 %

Sclérose en plaques[3] : biothérapies

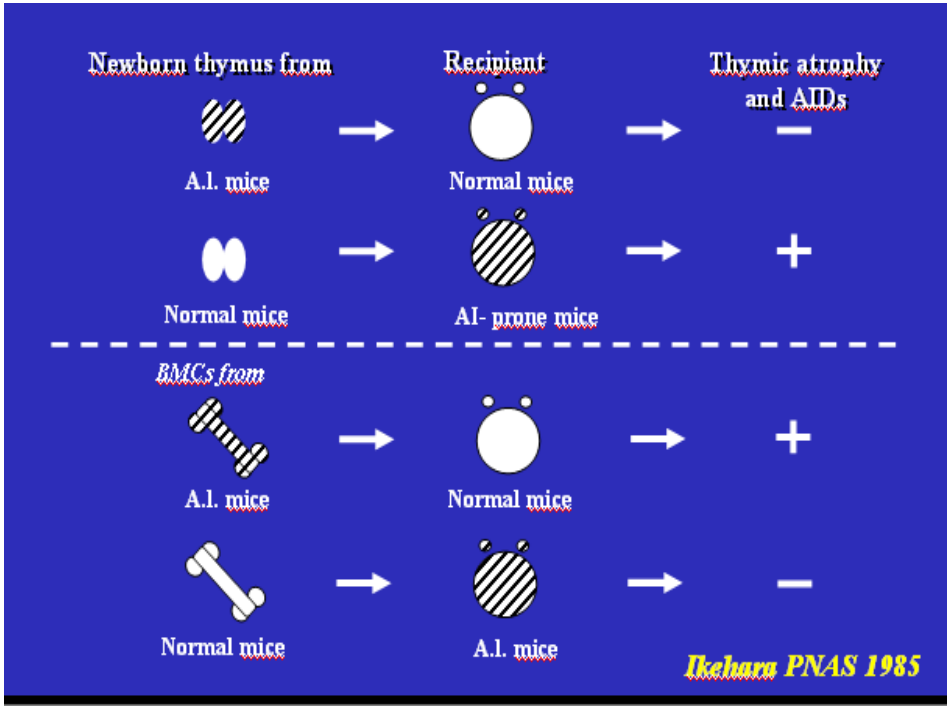
Crohn's[4] : immunosuppresseurs, immunomodulations

Diabète type I non acido-cétosique[5] : insuline à vie

1/ Farge D, et al. Bone Marrow Transplantation 2017;1-9. doi: 10.1038/bmt.2017.56. 2/ Illei GG, et al. Ann Rheum Dis 2011,70(12):2071-4. 3/ Muraro PA, et al. JAMA Neurol 2017;74(4):459-69. 4/ Lindsay JO, et al. Lancet Gastroenterol Hepatol 2017;2:399-406. 5/ Snowden J, et al. Bone Marrow Transplant 2012;47:770-90.

BM ? Treat AD in human *IKEHARA PNAS 1985*

T cell dysfonction <= thymic involution AD mice + aN HSC



1985: first succes allo BM in SLE mice
Imporved results with fetal BM: **stroma cells ? CSM** ?

Autoimmune strain	Disease	Effect
NOD	Diabetes	Resolution of insulinitis
B/W, BXSB	Glomerulonephritis	Regression of glomerular damage; reduction in circulating immune complexes or complete cure
MRL/lpr	Glomerulonephritis	Complete cure
MRL/lpr	Glomerulonephritis and arthritis	Complete resolution of glomerulonephritis arthritis and correction of immunological abnormalities
Old MRL/+	Pancreatitis and sialoadenitis	Cure of pancreatitis and sialoadenitis, normalization of T- and B-cell functions

V BEKKUM Best Pract Res 2004

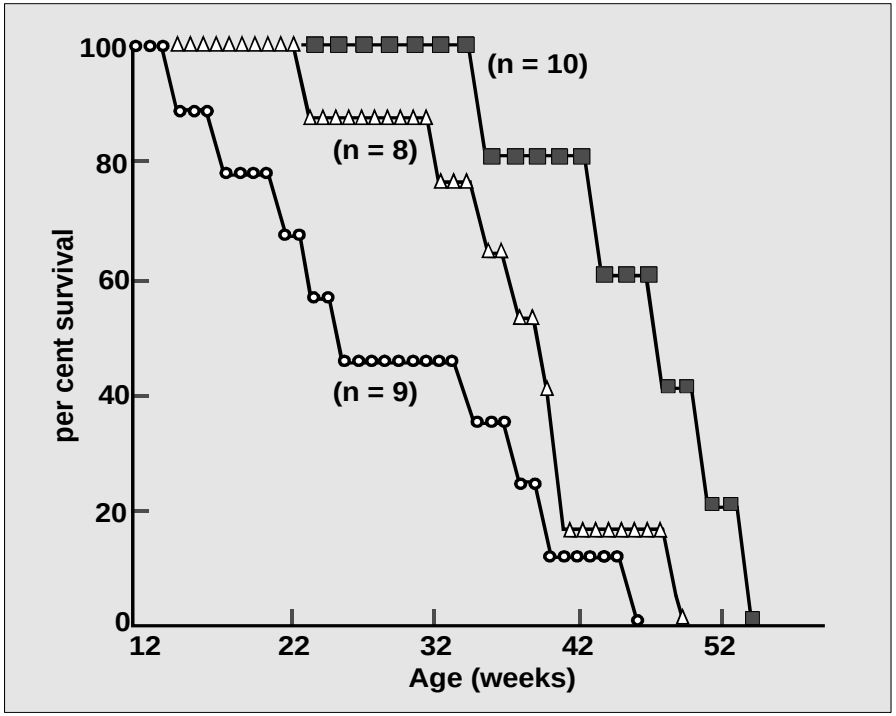
Disease	Effect
Adjuvant arthritis[a] (rats)	Complete remission
Collagen induced arthritis[a] (mice)	No remission, complete prevention of progression
Experimental allergic encephalomyelitis[b] (rats)	Complete remission, few relapses
Biozzi mice[a]	
Treated in acute phase:	Complete remission, few relapses
Treated in chronic phase:	No effect

Immunomodulation of AI in MRL/Lpr mice with syngeneic BMT

Karussis Clin Exp Immunol 1995; 100: 111

SLE associated mortality with:

- **Untreated mice**
- **TBI + syngenic BM (+ spleen cells)**
- **-CY + TBI + syngenic BM (+spleen cells)**



VAN BEKKUM :

. Inflammatory AD ◄ initiated + maintained by activated T cells ***! Eliminate***

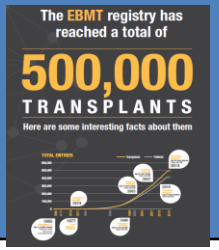
. Cy alone < Cy + TBI

. Relapse ◄ memory T cells ***! Radiation > Cy***

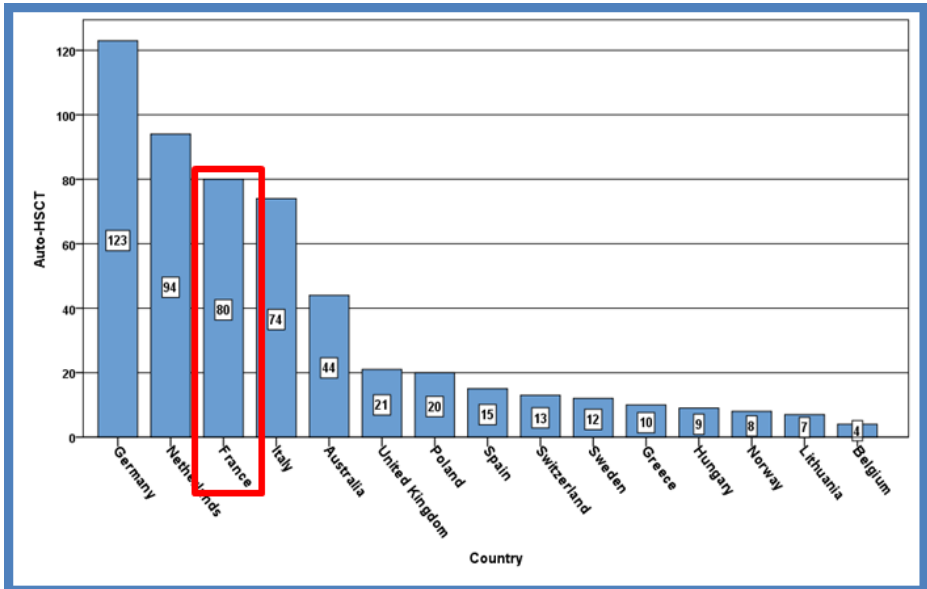
. Search for specific lymphocytolytic agents: Fludarabine , ATG?

. Immune reconstitution (? stem cell): recapitulation of ontogenesis

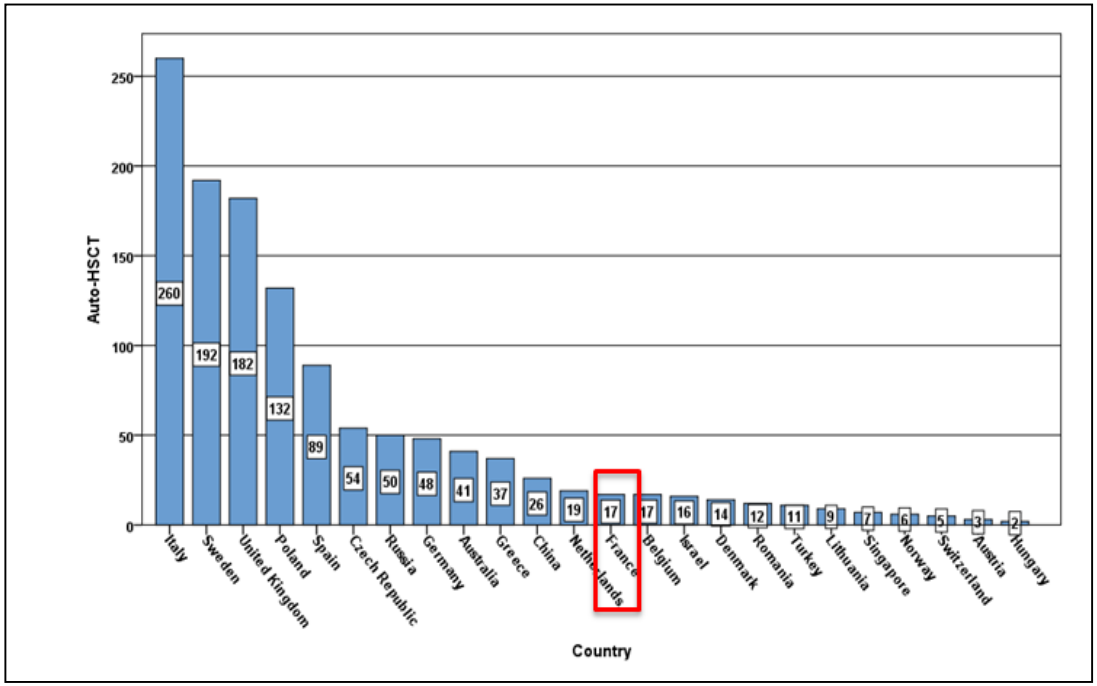
ADWP - Number of HSCT: 2754
EBMT Registry – September 2018



▶ **MULTIPLE SCLEROSIS**	**1271**
▶ **CONNECTIVE TISSUE**	**727**
SSc	553
SLE	116
PM-DM	18
Sjogren	5
Antiphosph. Syndrome	6
Other/Unknown	*29*
▶ **ARTHRITIS**	**186**
Rheumatoid arthritis	82
Juvenile chronic arthritis :	
**Systemic JIA*	59
**Other JIA*	18
**Polyarticular JIA*	17
Psoriatic arthritis	3
Other	*7*
▶ **INFLAMMATORY BOWEL**	**219**
Crohn's disease	181
Ulcerative colitis	4
Other	*34*
▶ **HAEMATOLOGICAL**	**113**
ITP	33
AIHA	26
Evans'	24
Other	30
▶ **VASCULITIS**	**56**
Wegener's	14
Behcet's	11
Takayasu	2
Polyarteritis	4
Churg-Strauss	2
Other/Unknown	23
▶ **OTHER NEUROLOGICAL**	**113**
NMO	26
CIDP	51
Myasthenia gravis	8
Other/Unknown	28
▶ **INSULIN DEPENDENT DIABETES**	**20**
▶ **OTHER**	**49**



France
3ème rang européen pour les autogreffes dans la sclérodermie



Haematopoietic stem cell transplantation (HSCT) in severe auto-immune diseases: updated guidelines written on behalf of the EBMT ADWP and PDWP

J Snowden, R Saccardi, M Allez, S Ardizzone, R Arnold, R Cervera, C Denton, JM van Laar, M Labopin, G Mancardi, R Martin, JJ Moore, J Passweg, C Peters, M Rabusin, M Rovira, D Farge

BMT 2011on line, free access

Per Ljungmann BMT 2009 Level II = **at least one well designed clinical trial without randomisation:** cohort or case controlled analytical studies (preferably > one centre), multiple time series studies

Disease	Sib donor	Well matched unrelated	Mismatched donor	Autologous
MS	D/III	GNR/III	GNR/III	CO / II
SSc	D/III	GNR/III	GNR/III	I
SLE	D/III	GNR/III	GNR/III	CO / II
Crohn's	GNR/III	GNR/III	GNR/III	CO / II
RA	GNR/III	GNR/III	GNR/III	CO/II
Vasculitis	GNR/III	GNR/III	GNR/III	CO/II
Polymyositis-Dermatomyositis	GNR/III	GNR/III	GNR/III	CO/II
CIPD	GNR/III	GNR/III	GNR/III	CO / II
Cytopenia	CO/II	D/III	GNR/III	CO / II
T1D	GNR/III	GNR/III	GNR/III	D / III
RCD Type II	GNR/III	GNR/III	GNR/III	D / III

Special report Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the EULAR and the EBMT A Tyndall and A Gratwohl **BMT 1997**

Systemic Sclerosis ? 1996-2018

Prevalence : **7 à 1580 / M** Incidence : **0.6 à 19 / million x 1.2 -1.8 black female**

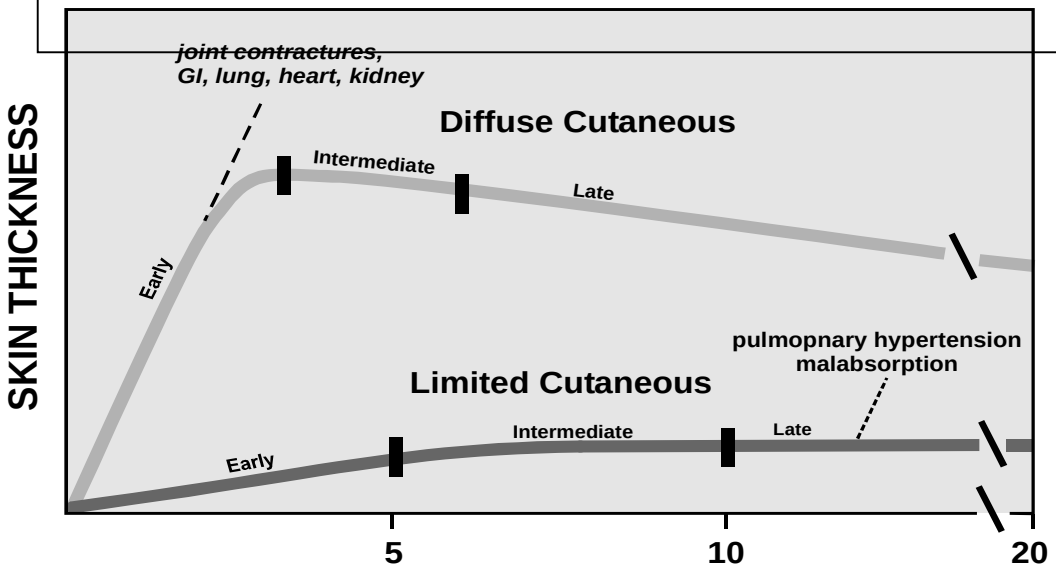
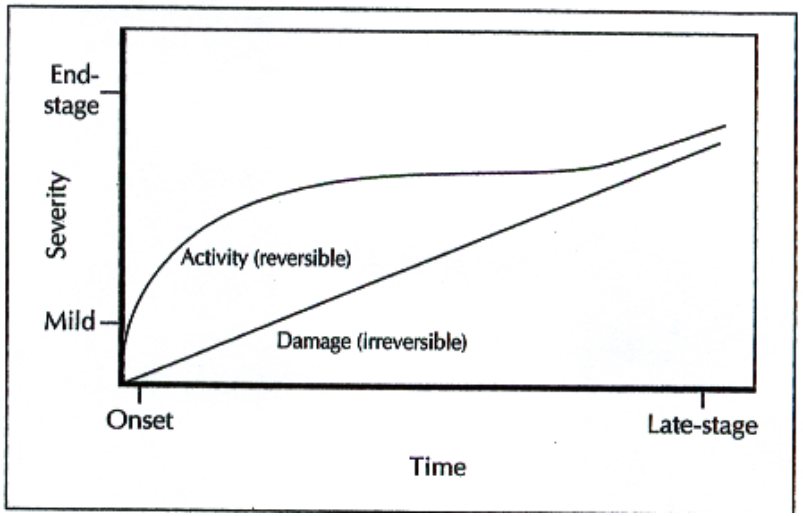


Figure 1. Schematic relation between disease damage and disease activity in systemic sclerosis



Clinical prediction of 5yr survival in SSC *Fransen J et al Ann Rheum Dis 2012* *www.eustar.org*

	Univariate		Multivariate	
	OR	p Value	OR	p Value
Age	1.04	< 0.0001	1.03	0.002
Male gender	2.55	< 0.0001	1.93	0.061
Presence of urine protein	2.9	0.0009	2.29	0.063
ESR ≥25 mm/h	2.83	< 0.0001	1.89	0.038
DLCO <70%	3.11	< 0.0001	1.94	0.033

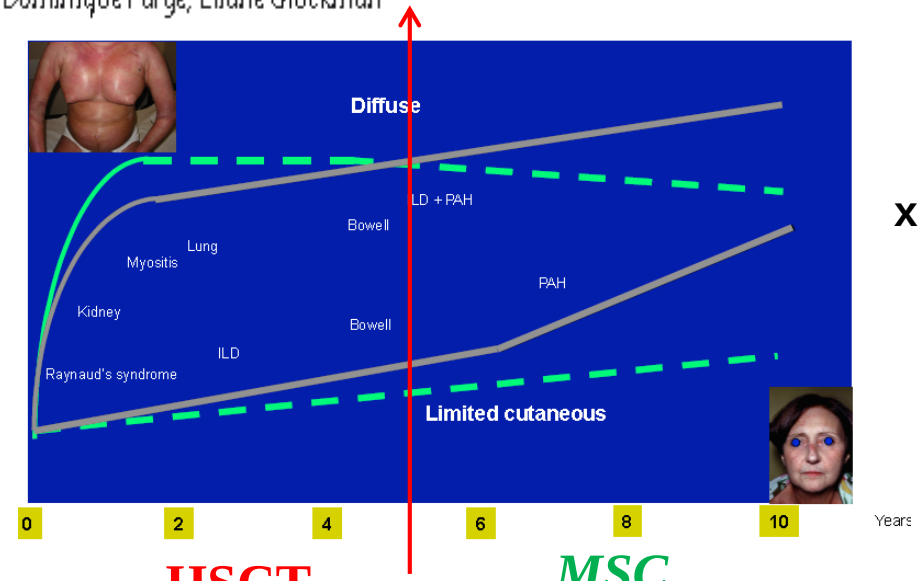
No of risk factors	Total no of patients	No of patients deceased	Mortality (%)	Mortality (%)
				Bryan *et al*[6]
0	509	12	2.2	7.1
1	349	45	12.9	22.8
2	168	55	32.7	54.8
3	23	7	30.4	100

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]

Autologous HSCT in systemic sclerosis: a step forward

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

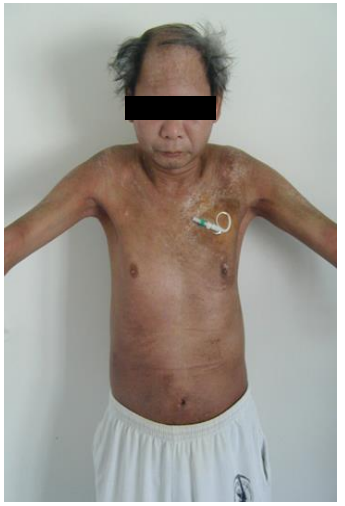
*Dominique Farge, Eliane Gluckman



HSCT ***MSC***

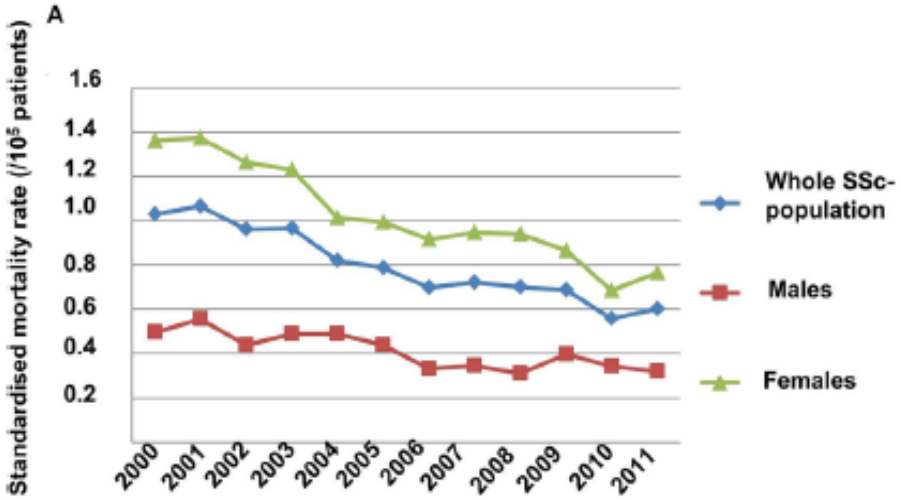
Prévalence 7–500 / Million

x 1.2 -1.8 femmes noires



1996--2018

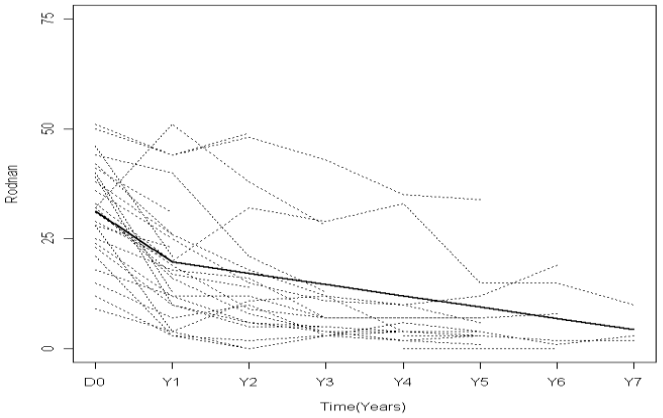
Taux Mortalité (SMR)
x 3.5 / population générale

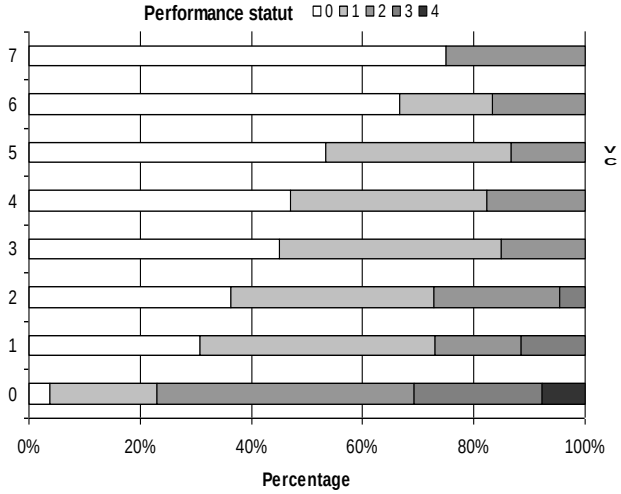


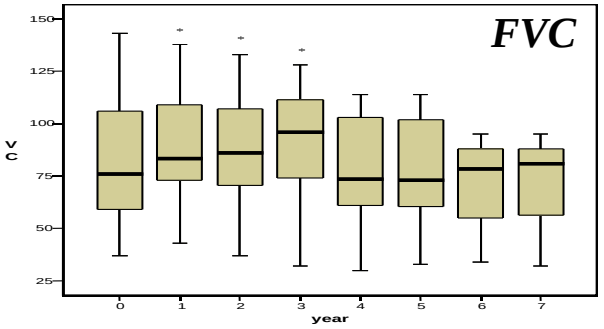
Elhai et al Ann Rheum Dis 2017

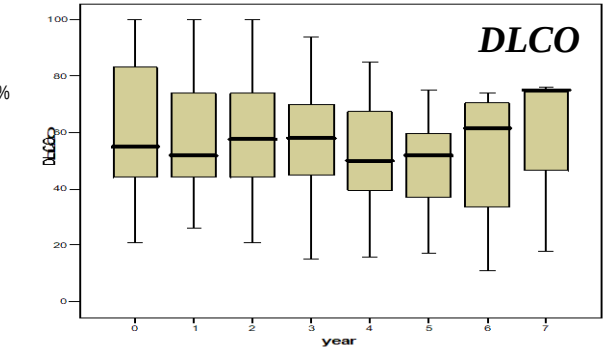
Fransen J et al Ann Rheum Dis 2012

CLINICO PATHOLOGICAL RESULTS from the phase I-II studies: Skin and lung fibrosis regression + Improved functionnal status

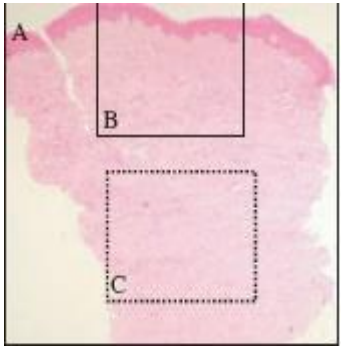


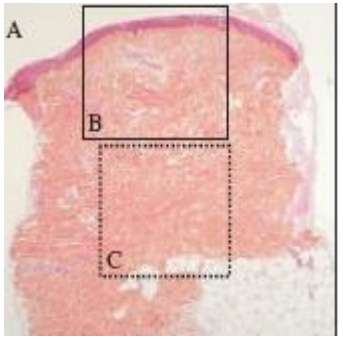




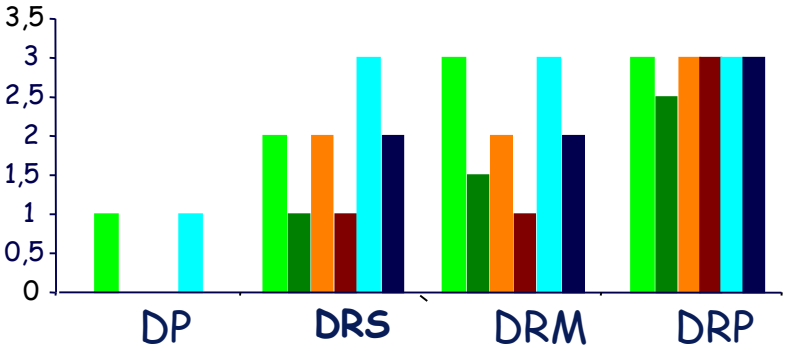


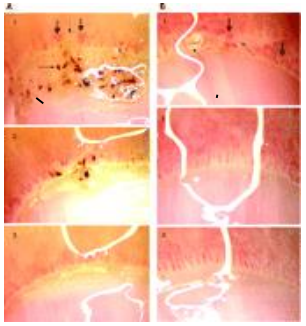
Farge et al BJH 002 , Ann Rheum 2004 , Vonk et al Ann Rheum 2008



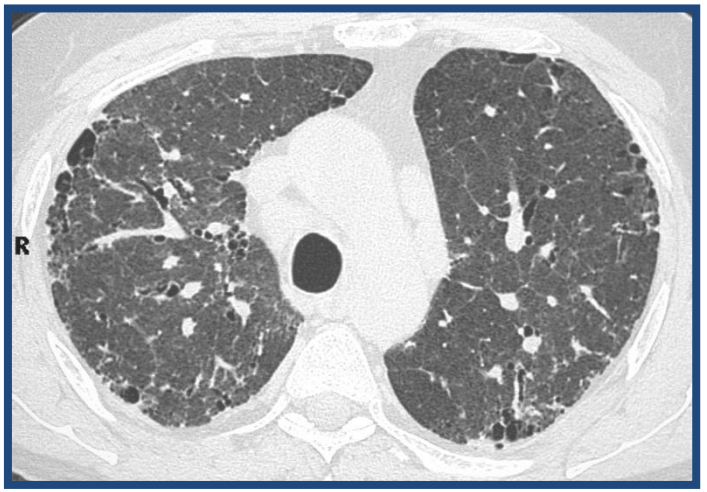


Verrecchia F , O Verola Rheumatology 2007





Aschwanden Daikeler et al ARD 2008



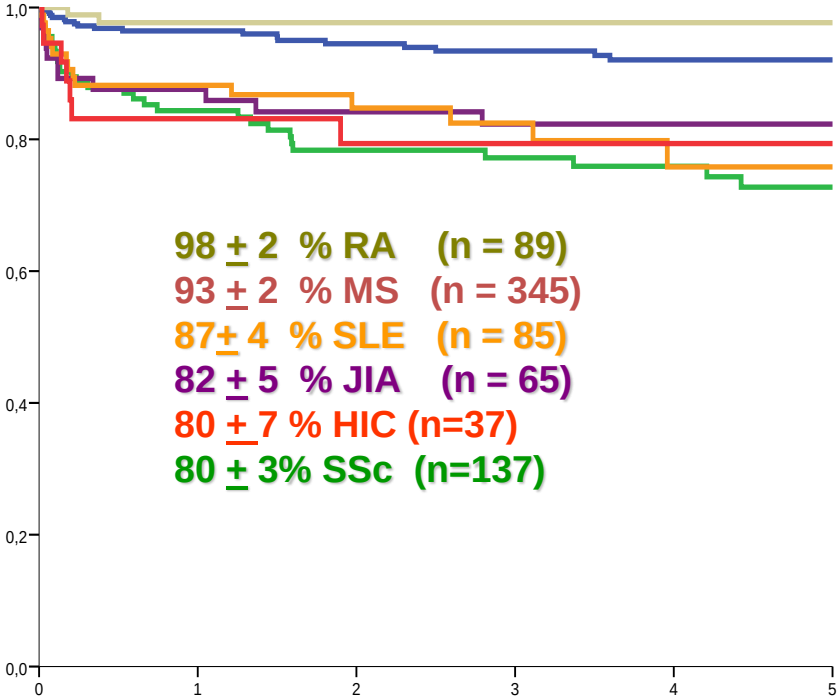
Launay D J Rheumatol 2009 scanner + CVF DLCO

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

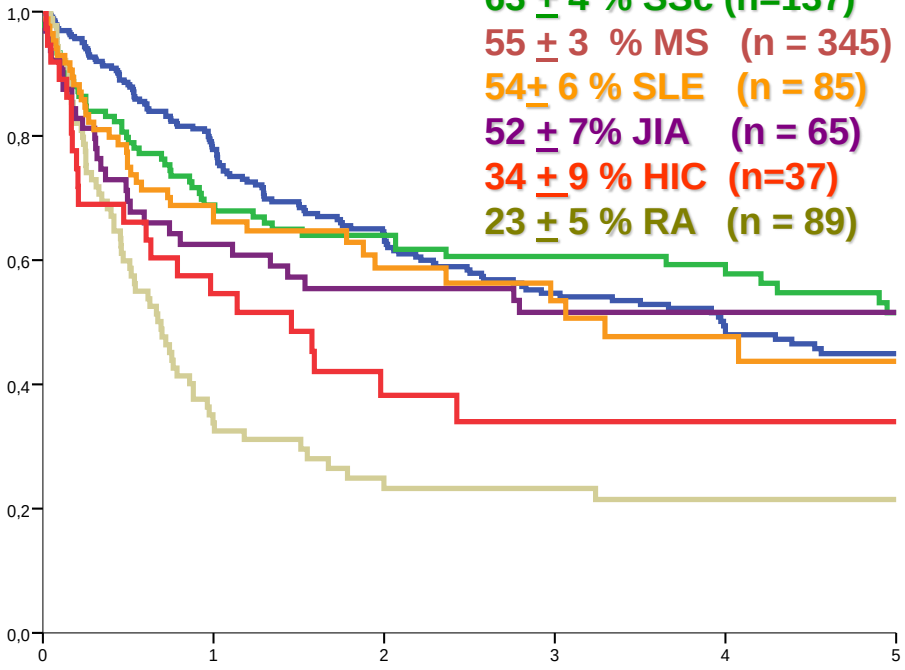
Dominique Farge,[1] Myriam Labopin,[2] Alan Tyndall,[3] Athanasios Fassas,[4] Gian Luigi Mancardi,[5] Jaap Van Laar,[6] Jian Ouyang,[7] Tomas Kozak,[8] John Moore,[9] Ina Kötter,[10] Virginie Chesnel,[11] Alberto Marmont,[12] Alois Gratwohl,[13] and Riccardo Saccardi[14]

haematologica | 2009; 95(2)

Overall Survival 3 yrs (n= 900)



PFS 3 yrs (n=900)



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

100 D TRM for SSC : 6 %

in 2017: 500 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

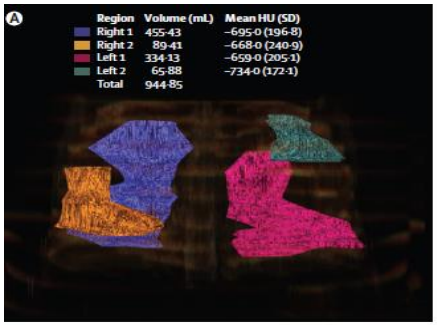
Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

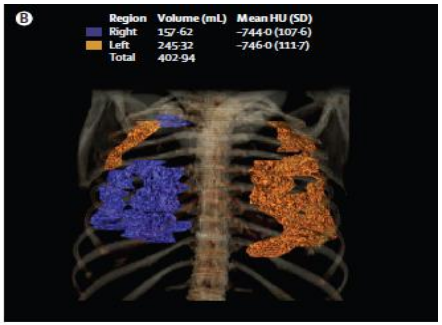
Lancet 2011; 378: 498–506

Richard K Burt, Sanjiv J Shah, Karin Dill, Thomas Grant, Mihai Gheorghiade, James Schroeder, Robert Craig, Kirk Hirano, Karin Marshall, Eric Ruderman, Borko Jovanovic, Francesca Milanetti, Sandeep Jain, Kristin Boyce, Amy Morgan, James Carr, Walter Barr*

Age (years)	45 (32–58)	44 (26–54)
Sex (female)	9	8
Ethnicity		
White	7	8
Hispanic	1	0
Black	2	1
Disease duration from diagnosis (months)	13·6 (2–33)	18 (6–36)
History of Raynaud's	9	9
Modified Rodnan skin score	28 (6–48)	19 (4–45)
Systemic sclerosis		
Diffuse	8	7
Limited (with lung involvement)	2	2
Gastrointestinal		
Gastrointestinal reflux disease	10	9
Patulous (gaping) oesophagus	6	5
Small bowel involvement	1	0
Lung		
Forced vital capacity	62% (53–70)	67% (43–84)
Diffusing capacity of CO_2 corrected	58% (29–82)	75% (29–111)
Involvement on high-resolution chest tomography	7	8
Non-specific interstitial pneumonia	6	8
Usual interstitial pneumonia	1	0
Bronchiectasis	1	0
Honeycombing	1	0
Nodules or micronodules	0	3
Cardiac		
Abnormal electrocardiogram	8	2
Tricuspid annular plane systolic excursion (cm)	2·24 (NA)	2·42 (NA)
Cardiac catheterisation		
Pulmonary artery systolic pressure (mm Hg)	29 (4·5)	28 (6·9)
Mean pulmonary artery pressure (mm Hg)	20 (4·0)	19 (4·8)

	Before switch to transplantation				
	Cyclophosphamide group (n=9)		Transplant group (n=10)		p value
	Baseline	1 year	Baseline	1 year	
Predicted forced vital capacity (%)					
Mean (SD)	67% (17·0)	61% (19·8)	62% (15·0)	74% (15·7)	0·004
Median (range)	78% (43–84)	69% (35–83)	62% (36–85)	82% (52–96)	..
Rate of change (%)†	..	−9%	..	15%	0·006
Predicted total lung capacity (%)					
Mean (SD)	83% (14·8)	74% (18·7)	76% (14·6)	80% (17·9)	0·005
Median (range)	89% (59–99)	69% (45–95)	73% (57–102)	72% (62–104)	..
Predicted DLCO corrected for haemoglobin (%)					
Mean (SD)	75% (27·5)	74% (37·0)	58% (21·8)	69% (18·6)	0·36
Median (range)	80% (29–111)	73% (28–120)	58% (29–94)	67% (33–90)	..
Volume diseased lung (mL)‡					
Mean (SD)	877 (240·6)	985 (277·1)	823 (268·9)	551 (277·1)	0·001
Median (range)	961 (462–1195)	858 (808–1189)	850 (359–1095)	546 (240–1118)	..
Modified Rodnan skin score					
Mean (SD)	19 (13·7)	22 (14·2)	28 (13·6)	15 (7·9)	0·0004
Median (range)	16 (6–45)	22 (3–44)	30 (6–47)	16 (2–29)	..





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, Borko Jovanovic, Irene B Helenowski, Julio Voltarelli**

1 The main outcome was treatment-related mortality

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

2

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.

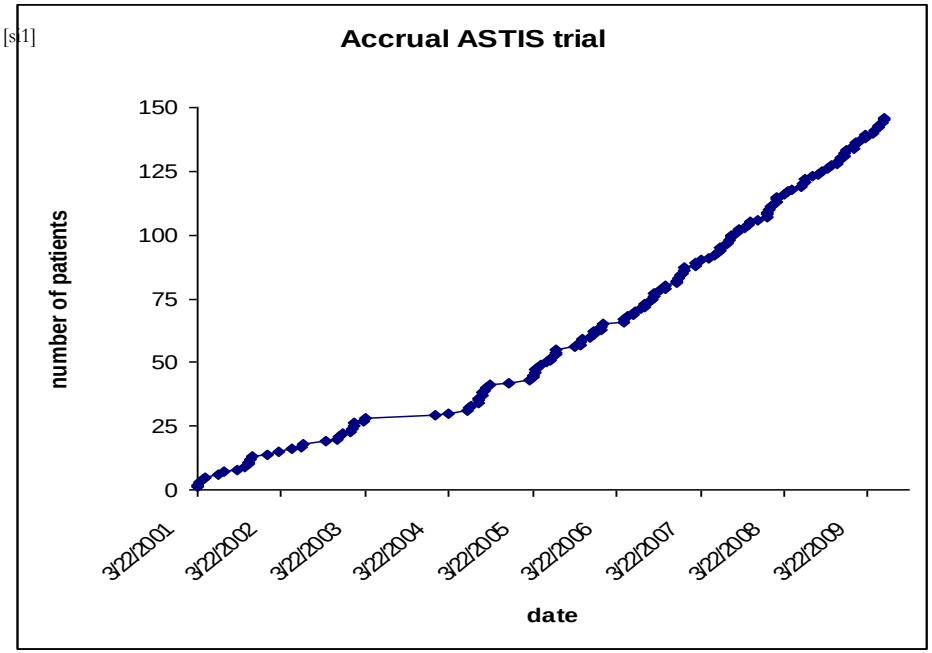
3

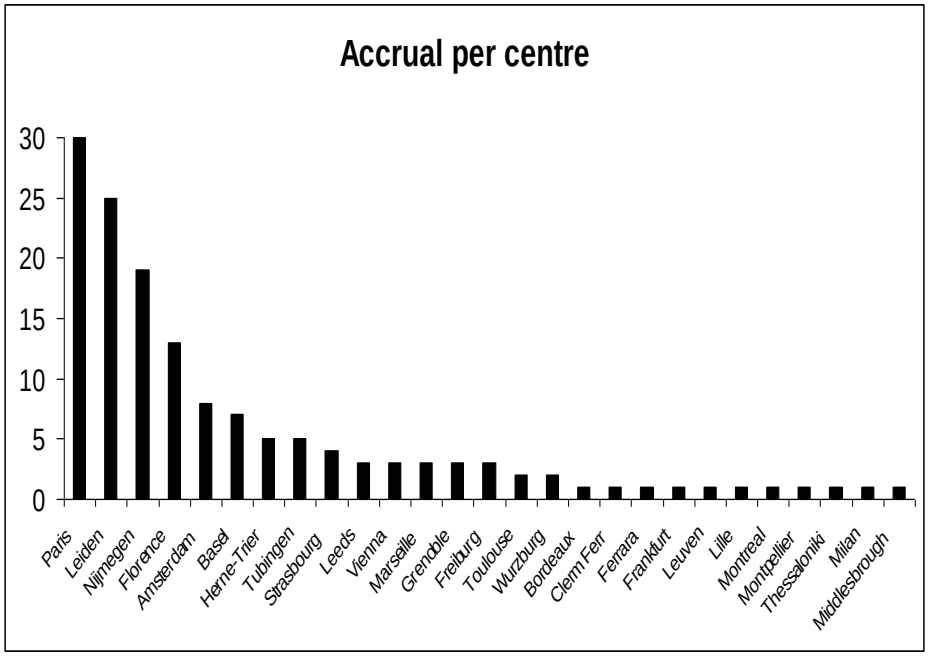
	Normal echocardiogram or electrocardiograph or female sex	Abnormal echocardiogram or electrocardiograph or male sex	p value*
DLCO			
Group: echocardiogram	Normal 71·3% (3·1)	Abnormal 56·7% (3·8)†	0·0045
Group: electrocardiograph	Normal 73·3% (4·6)	Abnormal 62·0% (3·0)‡	0·045
Group: sex	Female 66·3% (2·8)	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= update the 2004 EBMT guidelines

[s1]





156 SSc: 79 SCT+77 controles (27 centres)

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

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

RESEARCH COLLABORATION AGREEMENT **N° VAL / 2011/ 2011-070 /01 version 12 dec 2010-11**

BETWEEN: ASSISTANCE PUBLIQUE – HOPITAUX DE PARIS,

AND EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION

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

Original Investigation Research

Van Laar JVL and Farge D et al

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

Table Baseline Characteristic of Study Patients

Characteristic	All Patients (N=156)	Transplant Arm (N=79)	Control Arm (N=77)
Age - yr	43.8 (11.3)	44.2 (11.1)	43.3 (11.5)
Female sex – no. (%)	92 (59.0)	43 (54.4)	49 (63.6)
Disease Duration - yr	1.4 (1.3)	1.4 (1.2)	1.5 (1.4)
Major organ involvement – no. (%)			
Lung	135 (86.5)	68 (86.1)	67 (87.0)
Kidney	5 (3.2)	3 (3.8)	2 (2.6)
Heart	13 (8.3)	6 (7.6)	7 (9.1)
None	16 (10.3)	8 (10.1)	8 (10.4)
Current or past smoker– no. (%)	84 (53.8)	41 (51.9)	43 (55.9)
Pre-trial use of cyclophosphamide – no.	34 (21.8)	17 (21.5)	17 (22.1)
Weight (kg)	68.6 (14.4)	71.5 (15.2)	65.6 (12.9)
BMI	23.8 (4.1)	24.7 (4.1)	22.9 (4.0)
Modified Rodnan skin score (mRSS)	25.3 (8.0)	24.8 (8.1)	25.8 (7.9)
Creatinine clearance (mL/min)	76.7 (25.9)	76.8 (26.1)	76.5 (26.0)
LVEF by echo	64.9 (8.5)	64.7 (8.7)	65.1 (8.3)
VC (% of predicted)	81.4 (18.4)	81.7 (19.3)	81.1 (17.6)
DLCO (% of predicted)	58.5 (14.1)	59.3 (14.3)	57.7 (14.0)
HAQ score	1.35 (0.8)	1.25 (0.74)	1.44 (0.84)

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

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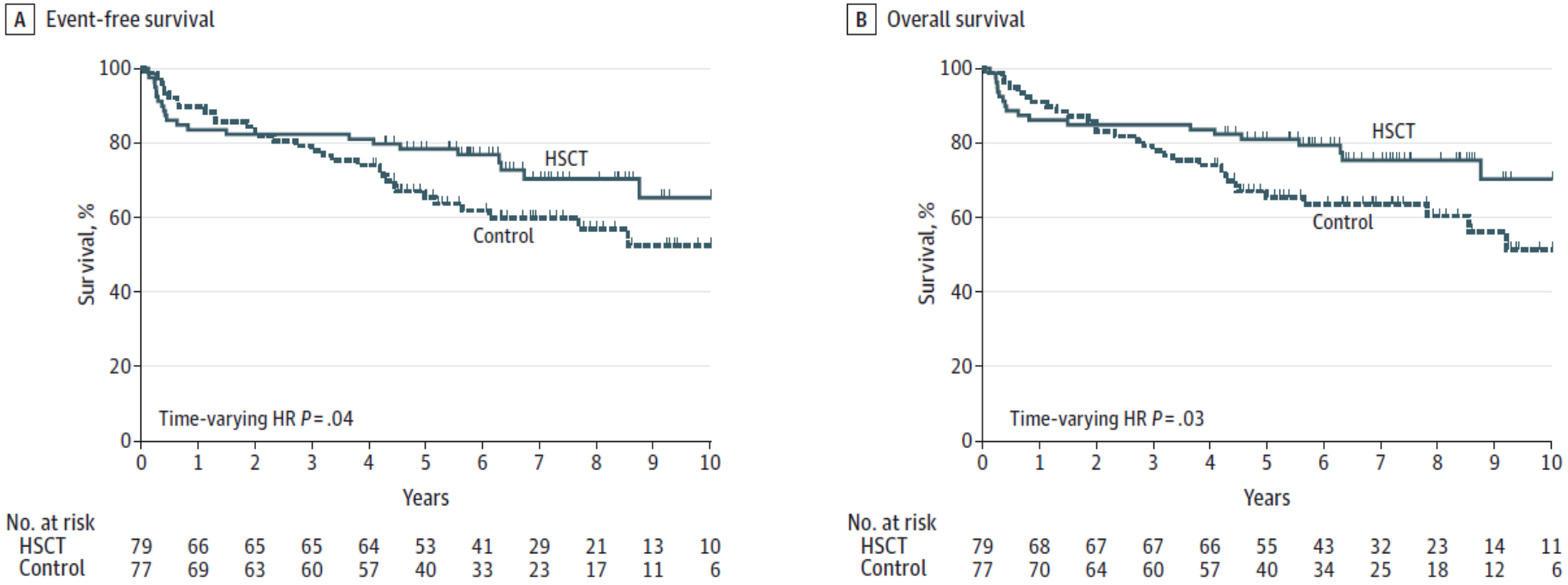
10% TRM in ASTIS: 15 yrs recruitement

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



Hazard ratios (HRs) and 95% CIs were calculated by Cox regression. Hazard ratios were time-varying. The hazard (slope of the survival curve) in the hematopoietic stem cell transplantation (HSCT) group is initially high because of treatment-related mortality but gradually improves. At 1-year follow-up, the HR already favors the HSCT group, which leads to the crossing of the survival curves at 2 years' follow-up. A, Three-month follow-up: HR, 2.01 (95% CI, 0.74-5.49); $P = .17$; 6-month follow-up: HR, 1.35 (95% CI, 0.62-2.96); $P = .45$; 1-year follow-up: HR, 0.52 (95% CI, 0.28-0.96); $P = .04$; 2-year follow-up: HR, 0.35 (95% CI, 0.16-0.74); $P = .006$; 3- through 10-year follow-up: HR, 0.34 (95% CI, 0.16-0.74); $P = .006$. B, Three-month follow-up: HR, 2.40 (95% CI, 0.75-7.67); $P = .14$; 6-month follow-up: HR, 1.50 (95% CI, 0.61-3.68); $P = .38$; 1-year follow-up: HR, 0.48 (95% CI, 0.25-0.91; $P = .02$; 2-year follow-up: HR, 0.29 (95% CI, 0.13-0.65); $P = .002$; 3- through 10-year follow-up: HR, 0.29 (95% CI, 0.13-0.64); $P = .002$.

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

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

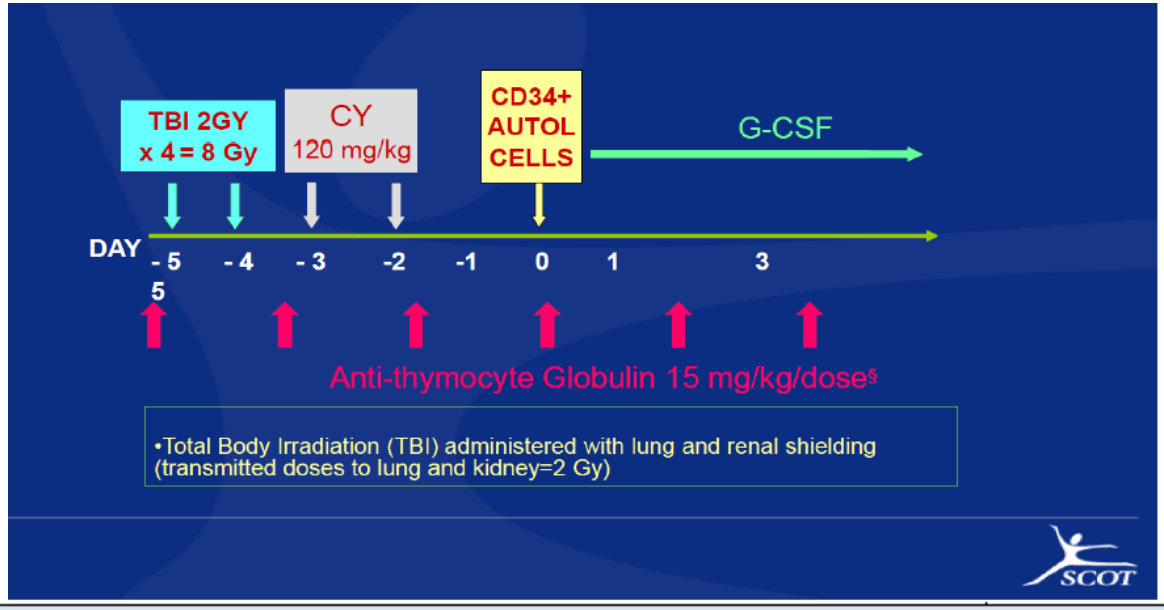
Variable	AUC, Mean (SD)		Difference (95% CI)	*P* Value
	HSCT Group (n = 67)[a]	Control Group (n = 64)[a]		
Weight, kg	-0.7 (9.5)	-0.8 (9.6)	-0.2 (-3.5 to 3.1)	.91
Modified Rodnan skin score	-19.9 (10.2)	-8.8 (12.0)	11.1 (7.3 to 15.0)	<.001
Creatinine clearance, mL/min[b]	-12.1 (29.7)	-1.2 (24.1)	10.9 (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

ASTIS CAUSES OF DEATH PLEASE READ THE ANNEX !!

JAMA. 2014;311(24):2490-2498.

Survival, days[b]	Survival after Transplant, days	Cause of Death	Autopsy	Relationship to Treatment[c]
153	11	progressive heart failure after HSCT, related to underlying SSc and treatment	not done	probably related
131	35	hemodynamic shock during ATG administration followed by ARDS, mesenteric ischemia, ATN and subsequently MOF	extensive fibrosis and pleural thickening, dilated cardiomyopathy, peripheral (but not coronary) atherosclerosis and ATN	definitely related
87	5	shock and subsequently ARDS	not done	definitely related
144	46	hemodynamic shock, EBV reactivation, PTLD, ATN, ARDS and subsequently MOF	malignant lymphoma in spleen and lymph nodes	definitely related

Cause of Death	Transplant Group (n=19)[a]	Control Group (n=30)
Disease progression	9 (47.4)	19 (63.3)
Treatment-related	8 (42.1)	0
Cardiovascular	0	4 (13.3)
Cerebrovascular	1 (5.3)	0
Hemato-oncological malignancy	1 (5.3)	5 (16.7)
Other[b]	0	2 (6.7)



	Hierarchy of component outcomes					Pairwise Comparisons Subject						
Subject	Mortality	EFS Failure	FVC	HAQ-DI	mRSS	1	2	3	4	5	6	GRCS
1	Dead (2 mo)					.	0	-1	-1	-1	-1	-4
2	Dead (50 mo)					0	.	-1	-1	-1	-1	-4
3	Alive	Yes (renal)	↓>10%	No Δ	↓>25%	1	1	.	-1	-1	-1	-1
4	Alive	Yes (lung)	↓>10%	↓>0.4	No Δ	1	1	1	.	-1	-1	1
5	Alive	No	No Δ	No Δ	↓>25%	1	1	1	1	.	-1	3
6	Alive	No	↑>10%	↓>0.4	No Δ	1	1	1	1	1	.	5

The GRCS is an analytic tool that accounts for multiple disease manifestations simultaneously but does not measure clinical disease activity or severity; it reflects how participants compare to one another based on a hierarchy of ordered outcomes. To compute the GRCS, each subject is first compared to every other subject and assigned a "pairwise comparison score" of 1 (better off), 0 (no different), or -1 (worse off). The table

COMBINING MORTALITY AND LONGITUDINAL MEASURES IN CLINICAL TRIALS *Statist. Med.* **18**, 1341–1354 (1999)

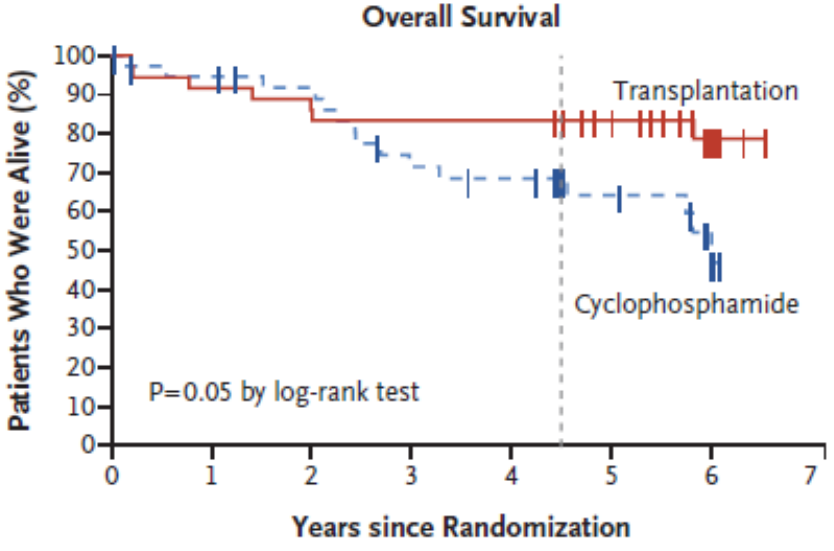
STATISTICAL ANALYSIS

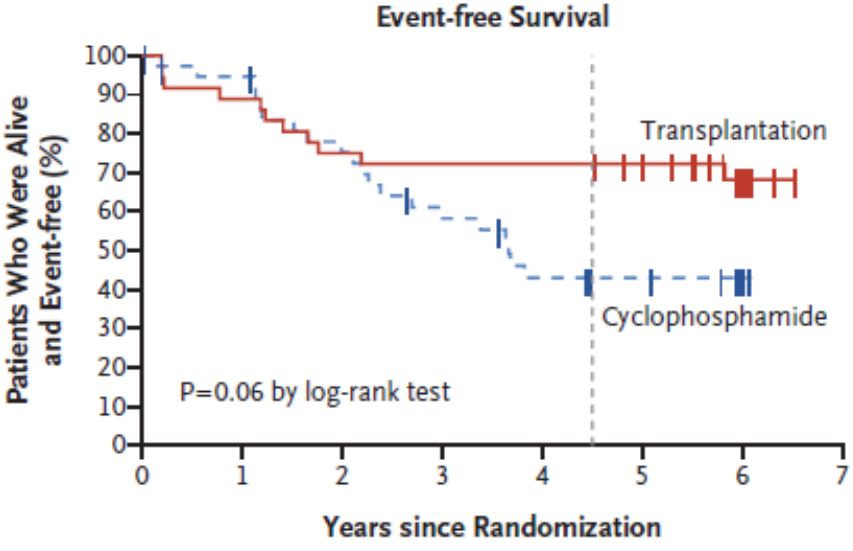
The trial was originally designed for 226 participants, with event-free survival as the primary end point. Low accrual prompted amendments, first to broaden entry criteria, then, ultimately, to reduce the sample size by changing the primary end point to the global rank composite score. Power for the new design with 114 participants.

board recommended stopping randomization at 75 participants.

Death from any cause — no. (%)			
By 54 mo	6 (17)	11 (28)	0.28
By 48 mo	6 (17)	11 (28)	0.28
Treatment-related death — no. (%)§			
By 54 mo	1 (3)	0	0.48
By 48 mo	1 (3)	0	0.48

C Intention-to-Treat Population





No. at Risk

Transplantation	36	33	31	30	30	25	9
Cyclophosphamide	39	35	32	24	22	15	7

	36	32	27	26	26	24	9
	39	35	27	20	14	12	6

Autologous HSCT is efficacious, but can we make it safer?

Richard K. Burt and Dominique Farge

NATURE REVIEWS | RHEUMATOLOGY
doi:10.1038/nrrheum.2018.34
Published online DD Mon 2018

Trial	Patients treated with HSCT (*n*)	Regimen	End points	HSCT-related deaths	Incidence of cancer	Overall survival
ASSIST	10	Non-myeloablative • CYC 200 mg/kg • rATG 6.5 mg/kg	Clinical improvement (mRSS or FVC) ($P = 0.00001$)	0%	0% (0 of 10)	100% (2 years)
ASSIST regimen	89	Non-myeloablative • CYC 200 mg/kg • rATG either 6.5 mg/kg or 4.5 mg/kg	• OS = 78% • RFS = 70% • mRSS ($P = 0.0003$) • FVC ($P = 0.004$)	6%	0% (0 of 89)	78% (5 years)
ASTIS	75	Non-myeloablative • CYC 200 mg/kg • rATG 7.5 mg/kg	• EFS ($P = 0.006$) • mRSS ($P < 0.001$) • FVC ($P = 0.004$)	10%	1.3% (1 of 75)	• 82% (5 years) • OS ($P = 0.002$)
SCOT	33	Myeloabaltive • TBI 800 cGy • CYC 120 mg/kg • eATG 90 mg/kg	EFS (2005–2010) • ITT ($P = 0.06$) • PP ($P = 0.02$) GRCS (after 2010) • ITT ($P = 0.01$) • mRSS (ITT, $P = 0.05$; PP, $P = 0.01$) • FVC (ITT, $P = 0.3$; PP, $P = 0.5$)	6%	9% (3 of 33)	• 86% (54 months) • 54 months OS ($P = 0.28$) • 72 months OS ($P = 0.02$)

CYC, cyclophosphamide; EFS, event-free survival; eATG, equine anti-thymocyte globulin; FVC, forced vital capacity; GRCS, global rank composite score; HSCT, haematopoietic stem cell transplantation; ITT, intention to treat; mRSS, modified Rodnan skin score; OS, overall survival; PP, per protocol; rATG, rabbit anti-thymocyte globulin; RFS, relapse-free survival; TBI, total body irradiation.

Indications et suivi des autogreffes de cellules souches hématopoïétiques dans les maladies auto-immunes et auto-inflammatoires : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

Bulletin du CANCER

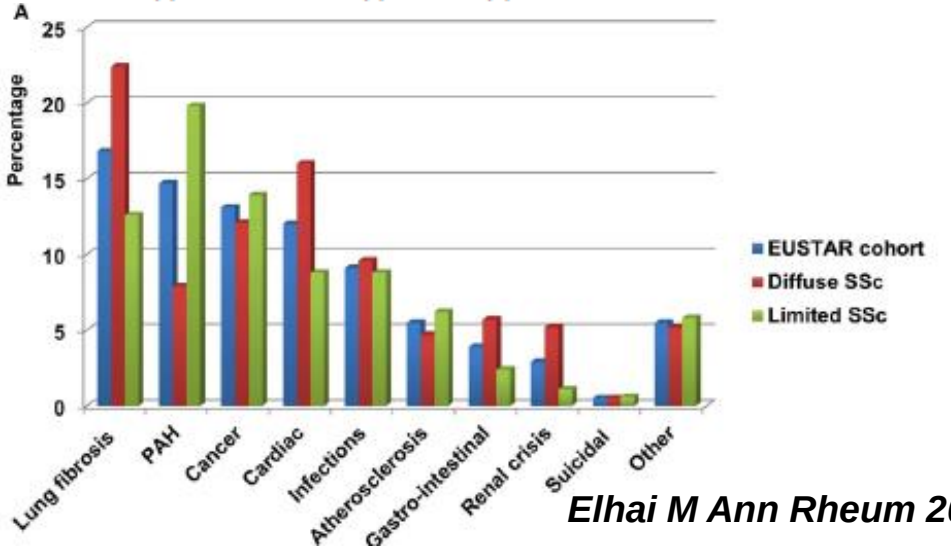
Grégory Pugnet [1], Christina Castilla-Llorente [2], Mathieu Puyade [3], Louis Terriou [4], Manuela Badoglio [5], Christophe Deligny [6], Perrine Guillaume-Jugnot [7], Céline Labeyrie [8], Ilham Benzidia [9], Hélène Faivre [9], Pauline Lansiaux [9], Zora Marjanovic [10], Jean-Henri Bourhis [2], Catherine Faucher [11], Sabine Furst [11], Anne Huynh [12], Thierry Martin [13], Patrick Vermersch [14], Ibrahim Yakoub-Agha [15], Dominique Farge [9]

Bull Cancer 2017; 104S: S169–S180

Contre-indications communes à l'autogreffe de CSH pour MAI

Les recommandations sont :

- âge > 65 ans ;
- tabagisme actif ou sevré depuis moins de 3 mois ;
- grossesse ou absence de contraception adaptée pendant toute la procédure et au moins trois ans après la greffe ;
- affection(s) concomitante(s) sévère(s) :



Elhai M Ann Rheum 2017

Sclérodermie systémique (SSc) (niveau d'évidence I) [6,8]

Les recommandations sont :

- âge entre 18 et 65 ans ; certaines indications pédiatriques, notamment chez l'adolescent, peuvent être discutées comme options thérapeutiques par un panel d'experts, incluant pédiatres hématologues et spécialistes de la SSc ;
- SSc diffuse ou limitée répondant aux critères diagnostics proposés par ACR/EULAR 2013 [9] avec une durée de la maladie depuis les premières manifestations viscérales (cutanées, cardiaques, digestives, pulmonaires ou rénales) hors Raynaud :
  - inférieure à 2 ans avec un phénotype clinique de SSc diffuse, un score de Rodnan modifié (mRSS) [10] supérieur à 20, une vitesse de sédimentation > 25 mm ou un taux d'hémoglobine inférieur à 11 g/dL, non expliquée par d'autres causes que l'évolutivité de la SSc, ou,
  - inférieure à 5 ans avec un mRSS > 15 associé à une atteinte viscérale sévère ou s'aggravant sur les 6 derniers mois : atteinte pulmonaire : une DLCO et/ou CVF inférieure à 80 % de la valeur théorique et atteinte interstitielle pulmonaire (atteinte bronchiolaire, plages de verre dépoli ou fibrose) sur la radiographie thoracique ou le scanner thoracique à haute résolution en coupes millimétriques ; atteinte rénale : hypertension artérielle, anomalies urinaires persistantes (protéinurie, hématurie, cylindres), anémie hémolytique micro-angiopathique, insuffisance rénale de novo, toute cause non liée à la SSc ayant été éliminée ; atteinte cardiaque : troubles du rythme auriculaires ou ventriculaires (épisodes récidivants de fibrillation ou flutter auriculaires, tachycardie atriale paroxystique, tachycardie auriculaire ou ventriculaire), bloc du 2ème et 3ème degré, épanchement péricardique, insuffisance cardiaque congestive régressive ; toute cause non liée à la SSc ayant été éliminée, ou,
  - inférieure à 5 ans avec un mRSS < 14 (atteinte cutané limitée) en cas d'atteinte pulmonaire sévère évolutive coexistante (altération de la CVF et/ou CPT $\geq$ 10 % et/ou de la DLCO $\geq$ 15 % par rapport à une valeur initiale obtenue 12 $\pm$ 6 mois auparavant).

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.

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

*Elie Mousseaux, MD, PhD
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Zora Marjanovic, MD
Rica Stanciu, MD
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Ludivine Perdrix, MD
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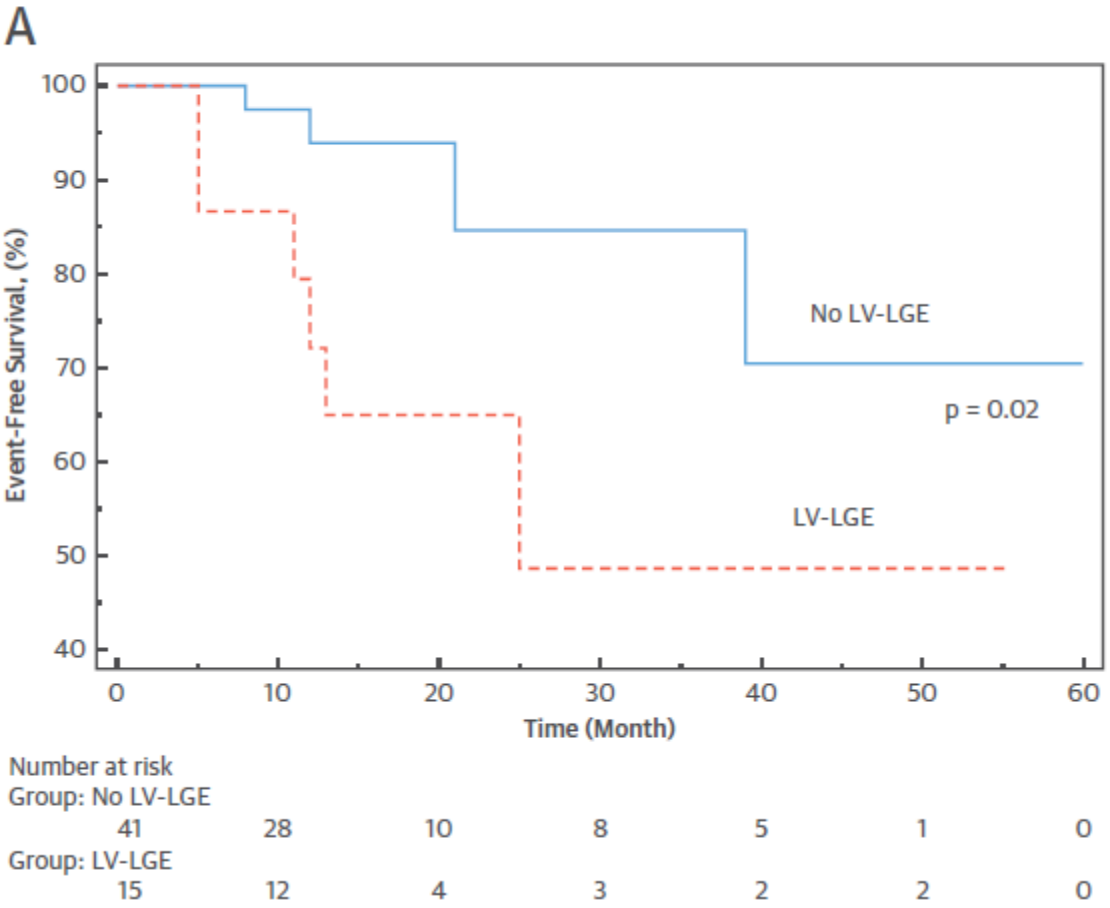
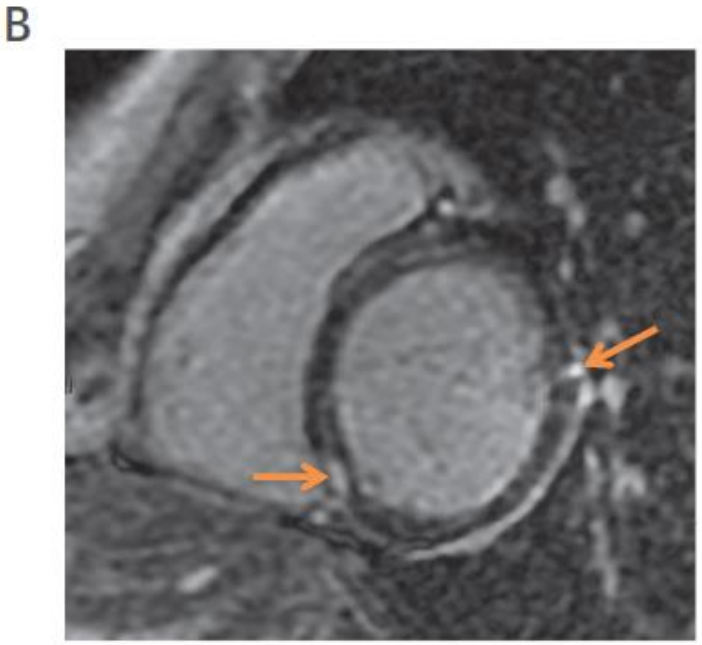
Gilles Soulat, MD
Dominique Farge, MD, PhD

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



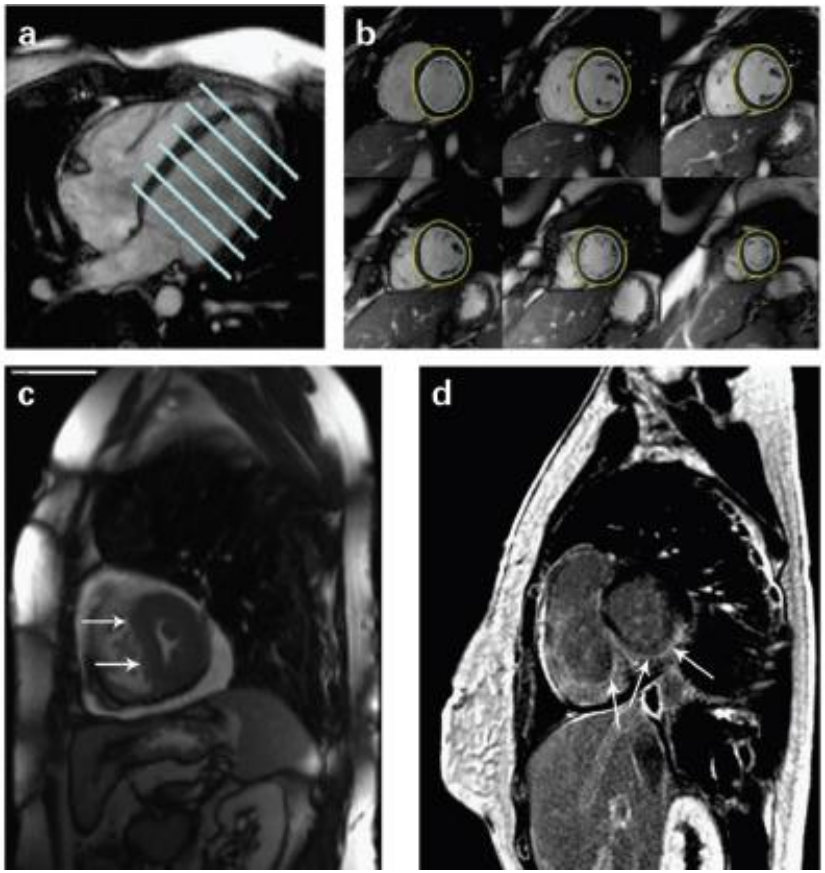


(A) Kaplan-Meier survival curves are shown of the time to event according to the presence (LV-LGE) or absence (No-LV-LGE) of left ventricular late gadolinium enhancement in CMR. **(B)** One case illustrates CMR presence of LV-LGE with a nodular pattern of focal enhancement at 2 different locations **(arrows)**.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

Cardiopulmonary assessment of patients with systemic sclerosis for hematopoietic stem cell transplantation: recommendations from the European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Party and collaborating partners

Bone Marrow Transplantation (2017)

ADWP EBMT , BRASIL AND CHICAGO



Intial screening

- Obtain medical records
- Speak with referring MD or complete questionnaire to confirm the presence of either dcSSc or lcSSc plus lung involvement

Appropriate candidate?

Yes

Invite for initial evaluation

- Lab testing: Cell blood count, Liver function tests, Basic chemistry panel, ANA, SCl-70, anti-polymerase III antibody, BNP (or NTproBNP)
- Pulmonary fuction testing
- High-resolution chest CT
- Electrocardiography
- Echocardiogram with doppler and tissue doppler plus dobutamine stress
- Cardiac MRI with contrast
- Cardiac catheterization with fluid challenge
- Holter monitor if history of palpitations or abnormal ECG
- Endoscopy if anemia or history of GAVE

No

Excluded From HSCT

Any cardiac exclusion criteria for HSCT?

- Baseline (resting) PASP > 40 mmHg or mPAP > 25 mmHg
- PASP > 45 mmHg or mPAP > 30 mmHg after fluid challenge
- Decrease or lack of augmentation of CO after fluid challenge
- Pulmonary vascular resistance > 3 Wood units
- D-sign of septal bounce on cardiac MRI
- LVEF < 45%
- Unrevascularized severe coronary artery disease
- Untreated severe arrhythmia
- Cardiac tamponade
- Constrictive pericarditis

Yes

No

Proceed with HSCT

Autologous stem cell transplantation for autoimmune diseases: Recommendations from the SFGM-TC

Bulletin du CANCER

Suivi des patients autogreffés

Date prévue				1 an		2 ans	Date prévue		3 ans		4 ans		5 ans
EXAMENS	M0	M3	M6	M12	M18	M24	EXAMENS	M30	M36	M42	M48	M54	M60
Examen clinique	X	X	X	X	X	X	*Examen clinique*	X	X	X	X	X	X
Indice OMS	X	X	X	X	X	X	Indice OMS	X	X	X	X	X	X
Scores spécifiques MAI	X	X	X	X	X	X	Scores spécifiques MAI	X	X	X	X	X	X
SSc : SHAQ, RODNAN							SSc : SHAQ, RODNAN						
SEP : EDSS							SEP : EDSS						
MC : CDAI							MC : CDAI						
LED : BILAG, SLEDAI							LES : BILAG, SLEDAI						
Consult. Stomatologique + panorex	X			X		X	*Consult. Stomatologique + panorex*		X		X		X
Consult ORL + Radiographies des sinus	X			X		X	*Consult ORL + Radiographies des sinus*		X		X		X
Consult ophtalmologie	X			X		X	*Consult ophtalmologie*		X		X		X
Consult gynécologique	X			X		X	*Consult gynécologique*		X		X		X
Bilans biologiques : hématologique, biochimique, immunologique, infectieux	X	X	X	X	X	X	*Bilans biologiques : hématologique, biochimique, immunologique, infectieux*	X	X	X	X	X	X
ECBU, protéinurie	X	X	X	X	X	X	*ECBU, protéinurie*	X	X	X	X	X	X
Sous-populations lymphocytaires	X	X	X	X	X	X	*Sous-populations lymphocytaires*	X	X	X	X	X	X
Sérothèque, Plasmathèque, DNAthèque	X	X	X	X	X	X	*Sérothèque, Plasmathèque, DNAthèque*		X	X	X	X	X
ECG	X	X	X	X	X	X	*ECG*	X	X	X	X	X	X
Echographie cardiaque	X	X	X	X	X	X	*Echographie cardiaque*	X	X	X	X	X	X
IRM cardiaque	X			X		X	*IRM cardiaque*		X		X		X
Radiographie pulmonaire	X	X		X	X	X	*Radiographie pulmonaire*	X	X	X	X	X	X
Test de Marche	X	X	X	X	X	X	*Test de Marche*	X	X	X	X	X	X
EFR + D_{LCO}	X		X				*EFR + D_{LCO}*	X	X	X	X	X	X
TDM pulmonaire	X		X				*TDM pulmonaire*	X	X		X		X
Ostéodensitométrie	X			X		X	*Osteodensitométrie*		X				X
Consultation diététicienne	X	X	X	X	X	X	*Consultation diététicienne*	X	X	X	X	X	X

Pugnet, Bulletin du Cancer 2017. PNDS 2018

ACTUALITES

des CRMR Maladies Auto-Immunes Systémiques Rares,
Université Paris Descarte, Paris, France

• 15 au 17 février 2018

5th Systemic sclerosis world congress,
Bordeaux, France

• 18 au 31 mars 2018

44th Annual meeting of the

AGENDA

R.C.P. MATHEC

Descriptif

La RCP est une réunion de concertation pluridisciplinaire réunissant différents spécialistes des maladies auto-immunes et auto-inflammatoire (interniste, neurologue, rhumatologue, hématologue, etc.) dans le but de discuter des différentes stratégies thérapeutiques qui s'offrent aux patients MAI. La décision du traitement le plus adéquat aux patients souffrant de MAI est prise de façon collégiale par ce groupe d'experts.

La présentation d'un patient au cours d'une RCP se fait via un formulaire qui doit être complété et retourné à l'adresse mail indiqué dans le formulaire au maximum la veille de la RCP. Les formulaires des patients qui seront présentés sont ensuite envoyés à tous les participants afin que chacun puisse avoir toutes les informations nécessaires à disposition pour discuter du cas.

Cette réunion a lieu tous les premiers mercredi du mois à 14h30. Un rappel de la réunion est effectué 8 jours et 3 jours avant la date de la réunion afin de pouvoir laisser le temps aux médecins spécialistes de remplir et de retourner le formulaire de présentation du patient.

Tous les intervenants, de tout horizon, désireux de participer à cette réunion sont les bienvenus.

Formulaire

Nous vous remercions de télécharger et de compléter ce formulaire pour chaque patient dont vous souhaitez que la situation soit examinée à la RCP « Thérapie cellulaire et MAI ».

Merci de nous faire parvenir le formulaire 8 à 3 jours avant la date prévue de la RCP par e-mail à l'adresse elodie.lemadre@aphp.fr , joignable au Tél : 01.42.38.50.93, ou par fax au 01.42.49.94.78 afin que nous puissions le diffuser à tous les participants.

PDF Adobe

Télécharger notre calendrier 2017 des RCP au format pdf

PDF Adobe

Calendrier annuel des RCP

✔ Mercredi 4 Janvier 2017 14h30 – 16h30
✔ Mercredi 1er Février 2017 14h30 – 16h00
✔ Mercredi 1er Mars 2017 14h30 – 16h00
✔ Mercredi 5 Avril 2017 14h30 – 16h00
✔ Mercredi 3 Mai 2017 14h30 – 16h00
✔ Mercredi 7 Juin 2017 14h30 – 16h00
✔ Mercredi 5 Juillet 2017 14h30 – 16h00

Pas de RCP au mois d'Aout

✔ Mercredi 6 Septembre 2017 14h30 – 16h00
✔ Mercredi 20 Septembre 2017 14h30 – 16h00
✔ Mercredi 4 Octobre 2017 14h30 – 16h00
✔ Mercredi 18 Octobre 2017 14h30 – 16h00
✔ Mercredi 8 Novembre 2017 14h30 – 16h00
✔ Mercredi 22 Novembre 2017 14h30 – 16h00
✔ Mercredi 6 Décembre 2017 14h30 – 16h00
✔ Mercredi 20 Décembre 2017 14h30 – 16h00

Connexion téléphonique

Participants :

1. Composer le numéro d'appel local du pays où vous vous situez (voir ci-dessous), pour la France c'est le 01 70 72 15 89

2. Puis entrer sur votre clavier téléphonique le code PIN Participant 110513 suivi de la touche #

3. Vous rejoignez la conférence audio

Nous vous remercions de télécharger les numéros d'accès par pays

PDF Adobe

Les compte-rendus des RCP MATHEC sont disponibles dans l'espace membre

POST AHSCT (AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION) MANAGEMENT FOR PATIENTS WITH SYSTEMIC SCLEROSIS: A PROSPECTIVE, NON-INTERVENTIONAL APPROACH ACROSS EUROPE « NISCC II

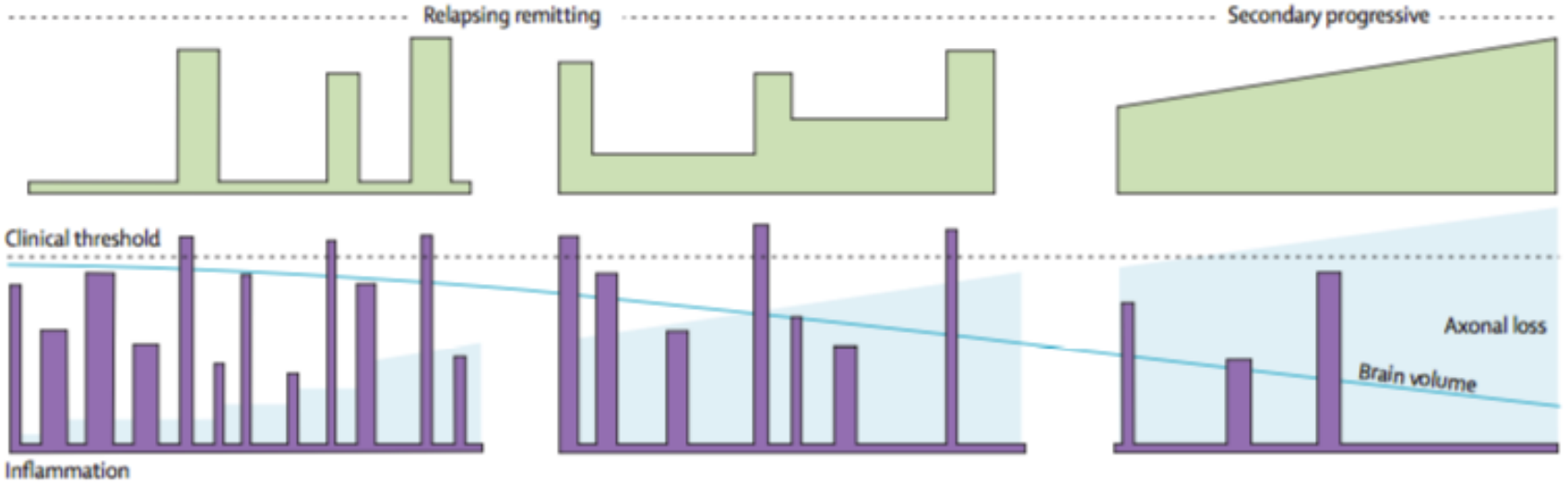
Sponsor	EBMT / ADWP

Study Identification Unique Protocol ID: ADWP 841001525
Brief Title: EBMT ADWP Prospective Non-interventional Study: Post-AHSCT Management in SSC Patients (NISSC-2)

Study Status
Record Verification: February 2018
Overall Status: Not yet recruiting Study Start: March 1, 2018 [Anticipated]
Primary Completion: December 31, 2019 [Anticipated]
Study Completion: March 30, 2020 [Anticipated]

Différentes formes évolutives : SEP-RR, SEP-SP, SEP-PP , SEP PR

Evolutivité : Activité + Progression=> aggravation du handicap



Lublin FD Neurology 1996 ; Neurology 2014

2017: critères Mc Donald

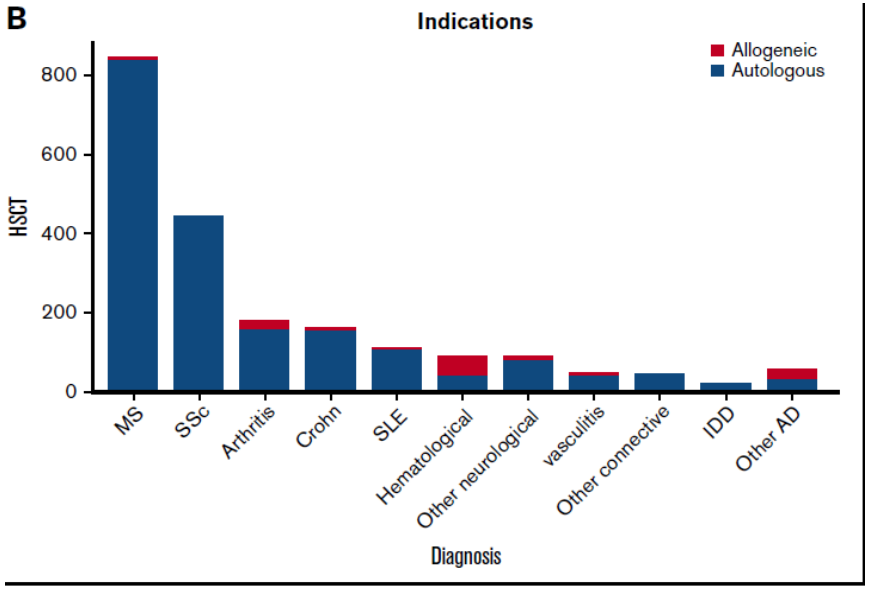
Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases

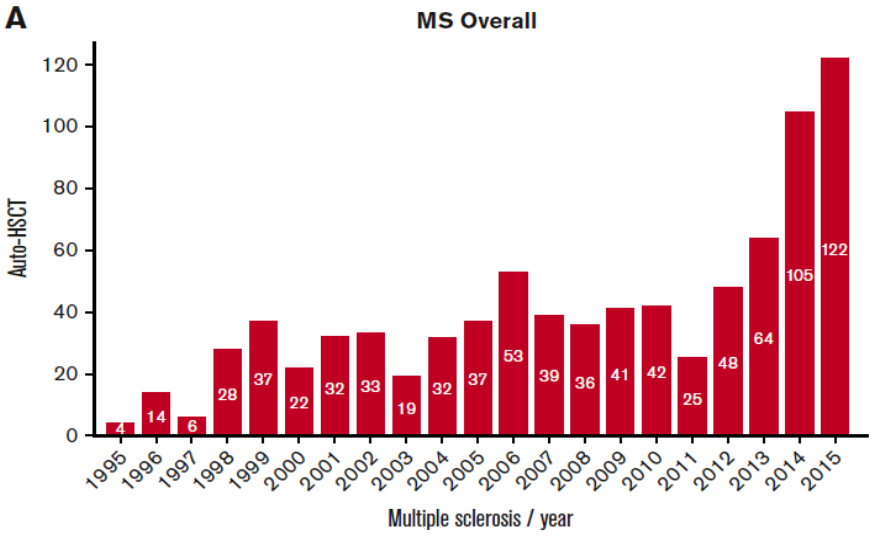
blood advances

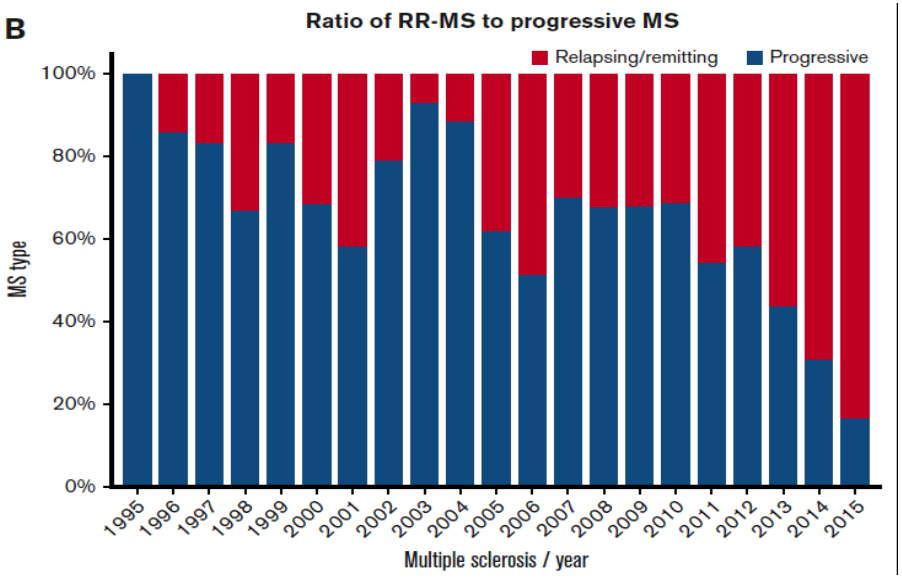
26 DECEMBER 2017 • VOLUME 1, NUMBER 27

John A. Snowden,[1] Manuela Badoglio,[2] Myriam Labopin,[3] Sebastian Giebel,[4] Eoin McGrath,[5] Zora Marjanovic,[6] Joachim Burman,[7] John Moore,[8] Montserrat Rovira,[9] Nico M. Wulffraat,[10] Majid Kazmi,[11] Raffaella Greco,[12] Emilian Snarski,[13] Tomas Kozak,[14] Kirill Kirgizov,[15] Tobias Alexander,[16] Peter Bader,[17] Riccardo Saccardi,[18] and Dominique Farge,[19,20] for the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP), EBMT Paediatric Working Party (PWP), and the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and EBMT (JACIE)

1994-2015: N= 1951 autogreffes







Autologous hematopoietic stem cell transplantation in multiple sclerosis

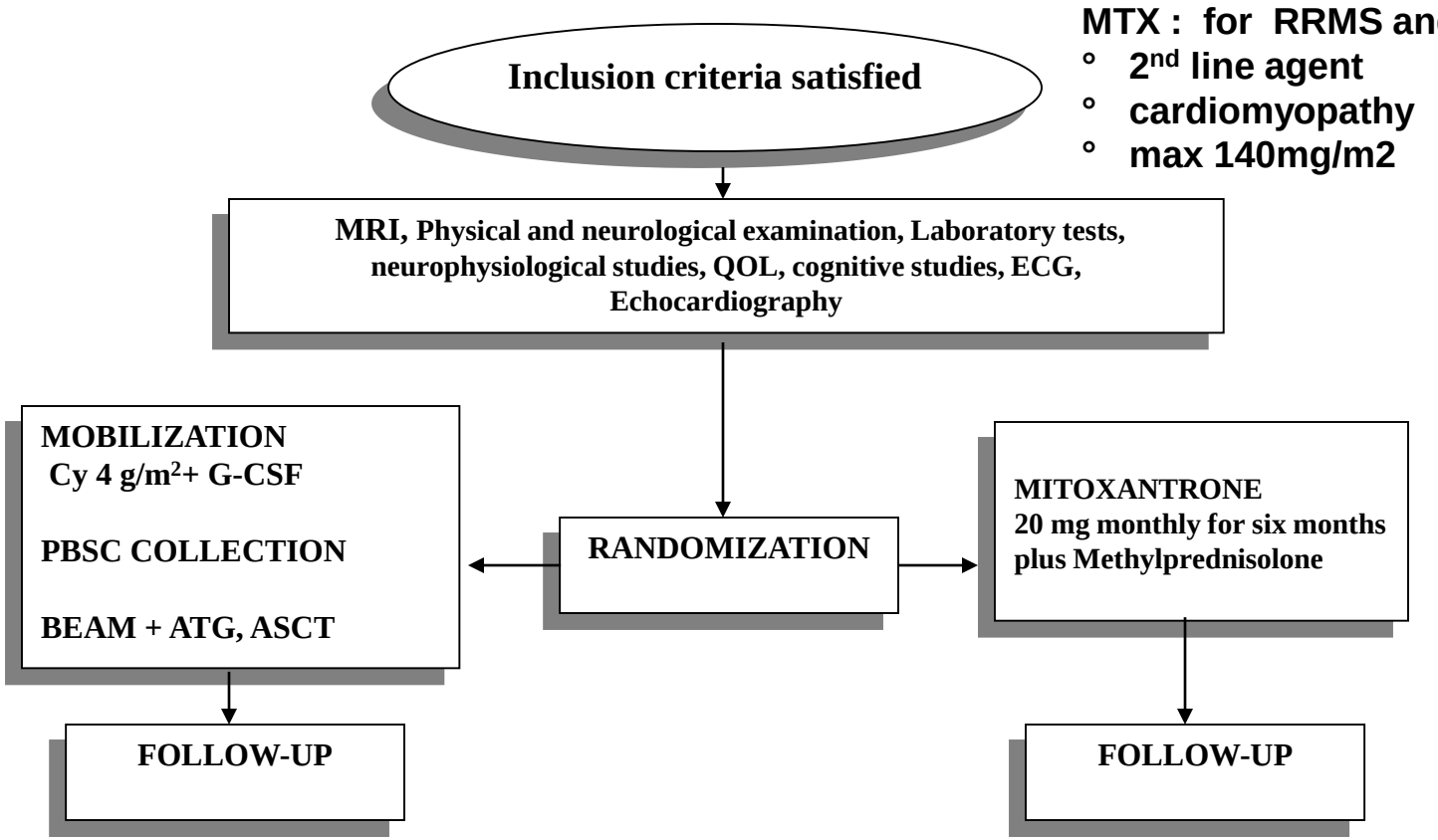
A phase II trial

Neurology® 2015;84:1-8

ASTIMS

Mancardi JL et al ADWP EBMT

HIGH DOSE IMMUNOABLATION AND AUTOLOGOUS STEM CELL TRANSPLANTATION VERSUS MITOXANTRONE THERAPY IN SEVERE MULTIPLE SCLEROSIS: a multicenter, prospective, randomized, phase II study.



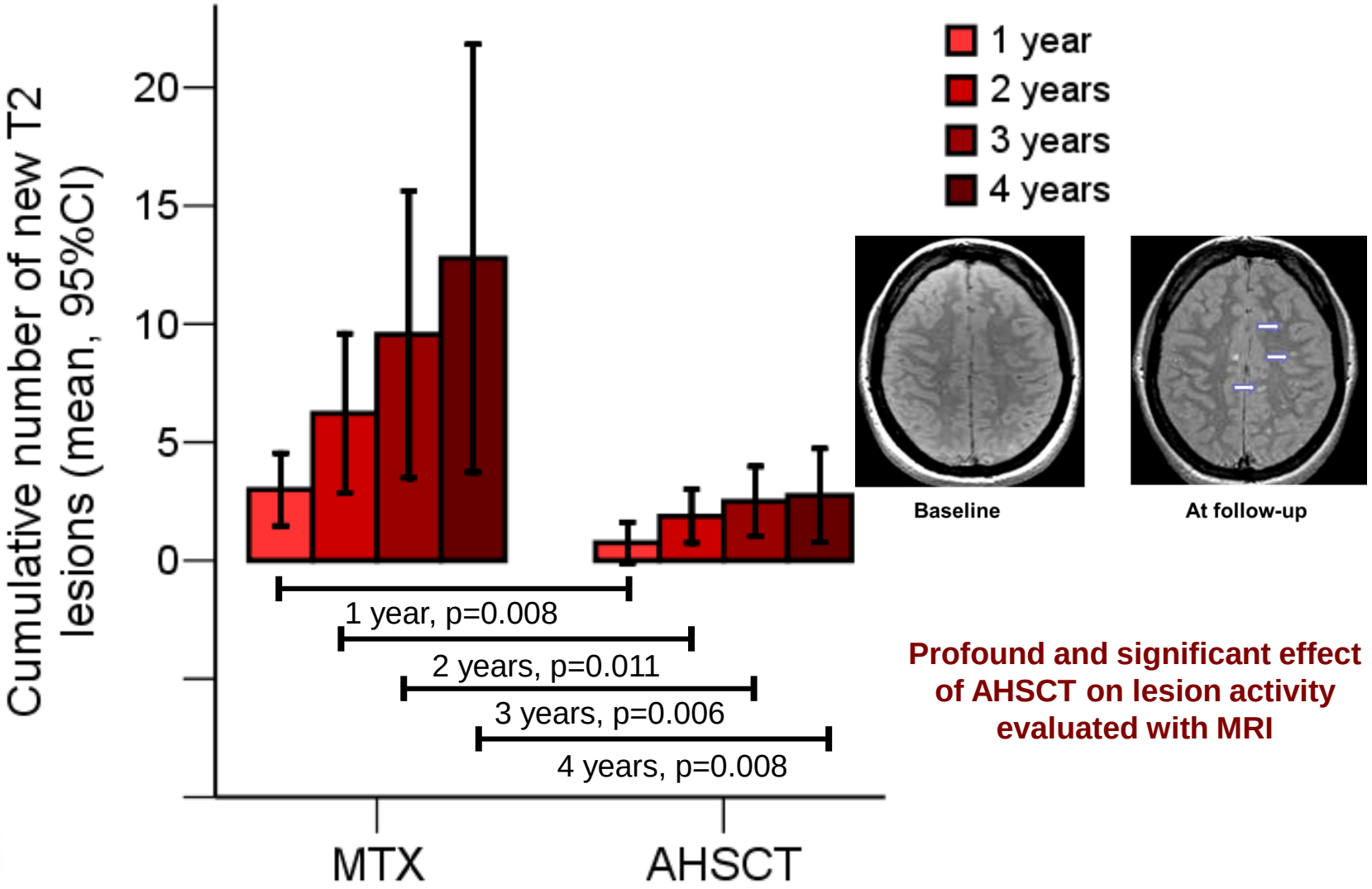
MTX : for RRMS and SPMS

- 2nd line agent
- cardiomyopathy
- max 140mg/m2

Cumulative nber of new T2 MRI lesions over 1,2,3 4 years

Mancardi et Al, Neurology 2015

Primary endpoint, ITT population



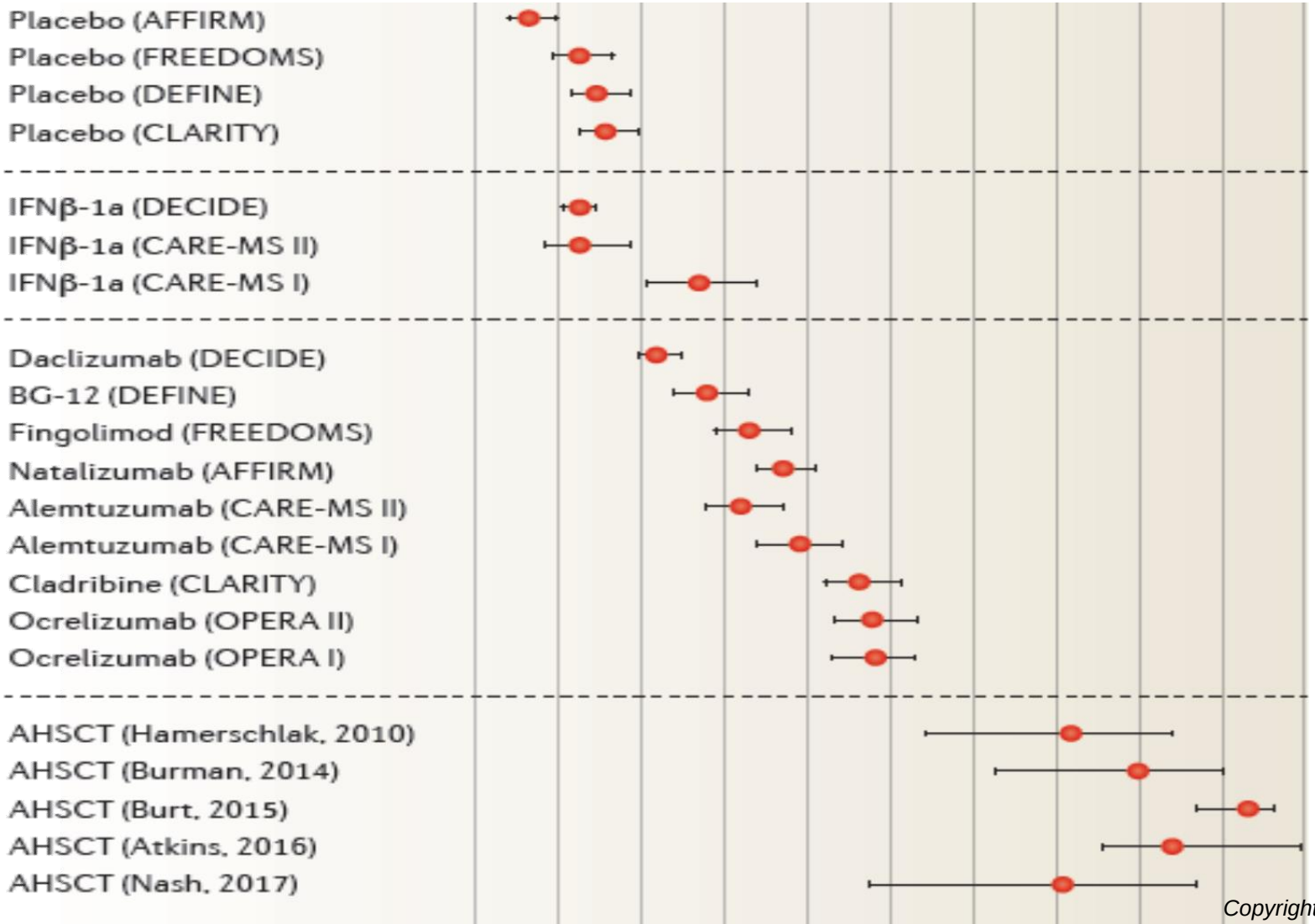
Profound and significant effect of AHSCT on lesion activity evaluated with MRI

No evidence of disease activity: new goals for RR-MS

Sormani MP, et al. Mult Scler 2017 ; Muraro PA, et al. JAMA Neurol 2017

No relapse No▲disability progression No new or active lesions on MRI

% of pts with NEDA at 2 years with



Quels PATIENTS SEP candidats à l autogreffe ?
McDonald 2010, < 60 ans avec score EDSS irréversible ≤ 6.0 et une ACTIVITE INFLAMMATOIRE

1) SEP -RR :

- Sous traitement de 2nde ligne bien conduit depuis au moins 6 mois,
- Au moins 1 poussée significative sur le plan clinique
- Augmentation d'un score EDSS de Kurtzke de ≥ 1 point , aboutissant à un score fonctionnel coté à plus de 2 pour le paramètre le plus affecté
- Au moins une prise de gadolinium sur une IRM de moins de 3 mois.

2) SEP -P :

- Sous traitement bien conduit de plus de 6 mois,
- Durée de phase progressive de moins de 5 ans,
- Au moins 1 poussée significative sur le plan clinique
- Au moins une prise de gadolinium sur une IRM de moins de 3 mois ou une nouvelle lésion T2 significative sur une IRM de moins de 3 mois comparée à une IRM de référence de moins de 1 an.

Original Investigation

Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease

A Randomized Clinical Trial

Twenty-three patients underwent HSCT and 22 received standard treatment (controls). There were no statistically significant between-group differences in proportions of patients achieving sustained disease remission, CDAI less than 150 in the last 3 months, or freedom from active disease; there was a statistically significant difference among patients able to discontinue active treatment in the last 3 months. There were 76 serious adverse events in patients undergoing HSCT vs 38 in controls; 1 patient undergoing HSCT died

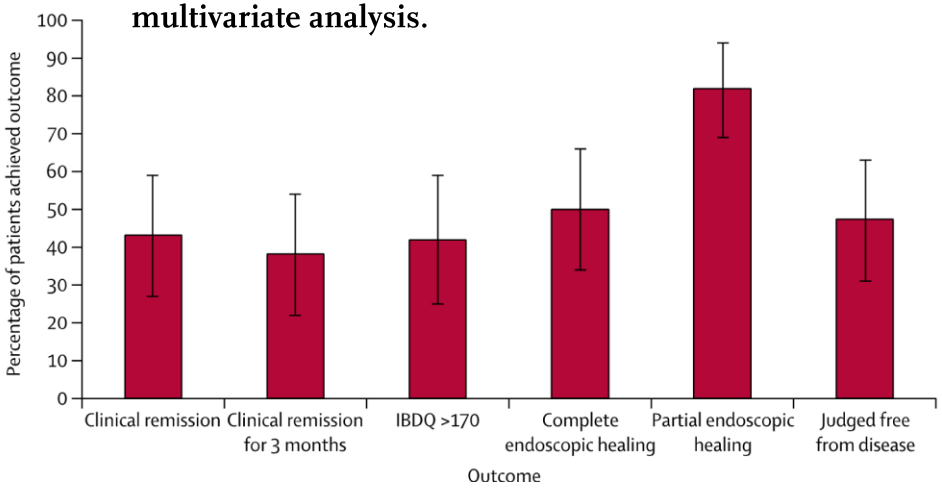
	No. (%)			
	HSCT	Control	Difference (95% CI), %	*P* Value
Sustained disease remission	2 (8.7)	1 (4.5)	4.2 (−14.2 to 22.6)	.60
Secondary outcomes				
No active treatment	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	.01
CDAI <150	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.052
Free of active disease	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.054

Hawkey J, et al. JAMA 2015;314(23):2524-34.

Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial

James O Lindsay, Mathieu Allez*, Miranda Clark, Myriam Labopin, Elenor Ricart, Gerhard Rogler, Montserrat Rovira, Jack Satsangi, Dominique Farge, Christopher J Hawkey, on behalf of the ASTIC trial group†, European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party, and European Crohn's and Colitis Organisation*

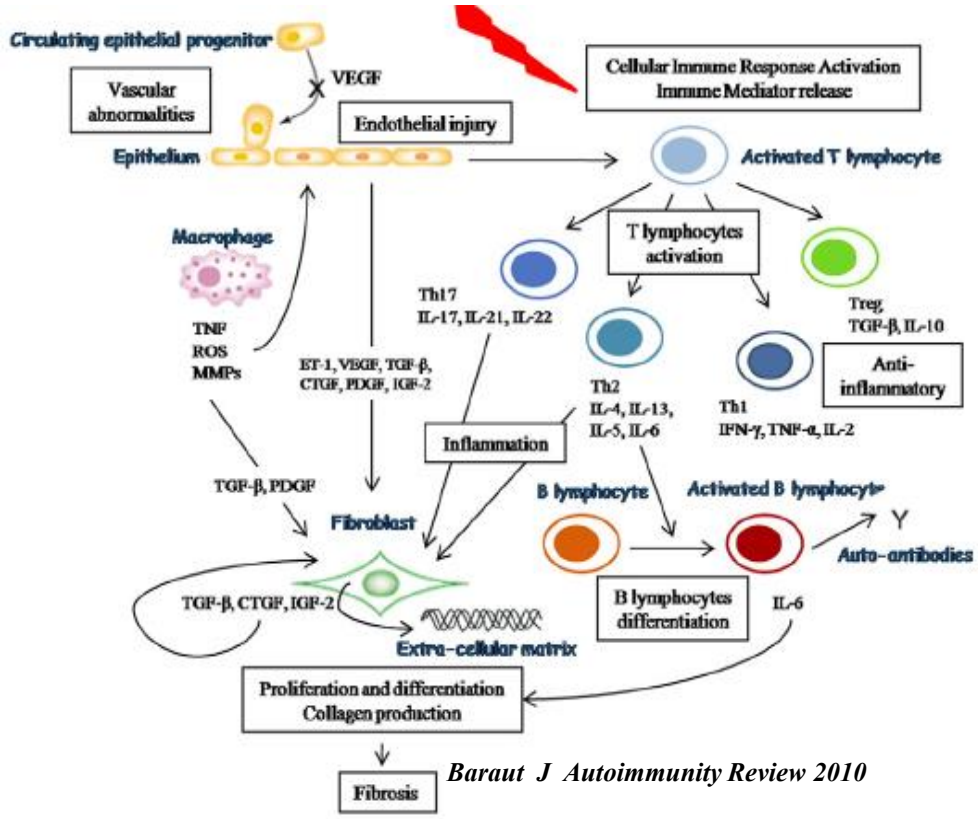
Findings Between June 28, 2007, and Sept 1, 2011, 45 patients were enrolled in the ASTIC trial from 11 European transplant units. 23 patients were randomly assigned to immediate HSCT, and 22 patients were assigned to mobilisation followed by conventional care. After completion of the ASTIC trial, 17 patients from the conventional care group received HSCT. In the combined cohort, data were available for 40 patients at baseline and 38 patients at 1 year after HSCT (one patient died, one withdrew). At 1 year after HSCT, 3-month steroid-free clinical remission was seen in 13 (38%, 95% CI 22–55) of 34 patients with available data for the whole year. Complete endoscopic healting was noted in 19 (50%, 34–66) of 38 patients. On multivariate analyses, factors associated with the primary outcome were short disease duration (odds ratio [OR] 0·64, 95% CI 0·41–0·997 per year; p=0·048) and low baseline CDAI (0·82, 0·74–0·98 per 10 units; p=0·031). 76 serious adverse events occurred in 23 of 40 patients with available data. The most common serious adverse event was infection, most of which were treatment related. Smoking and perianal disease at baseline were independent factors associated with the number of serious adverse events (OR 3·07 [95% CI 1·75–5·38; p=0·0001] for smoking and 3·97 [2·17–7·25; p<0·0001] for perianal disease) on multivariate analysis.



	Baseline	1 year	p value (paired)
CDAI (n=37)	336·73 (112·26)	195·95 (133·29)	<0·0001
PRO-2 (n=37)	24·03 (10·56)	12·45 (9·78)	<0·0001
EQ-5D index (n=27)	0·752 (0·104)	0·801 (0·164)	0·033
EQ-VAS (n=29)	53·55 (21·42)	72·72 (22·50)	0·00016
IBDQ (n=30)	119·57 (33·54)	152·23 (45·15)	<0·0001
SES-CD (n=36)	14·11 (9·03)	5·44 (6·57)	<0·0001

Lindsay JO, et al. Lancet Gastroenterol Hepatol 2017;2:399-406.

DETERMINANTS OF IMMUNE RESPONSE AFTER HSCT

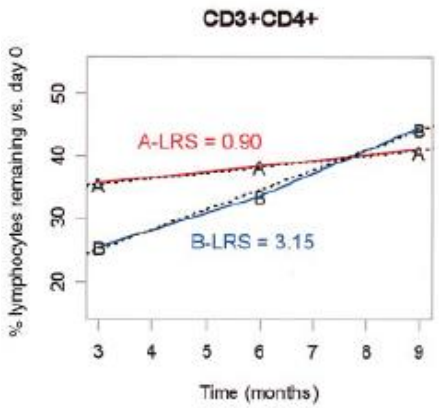


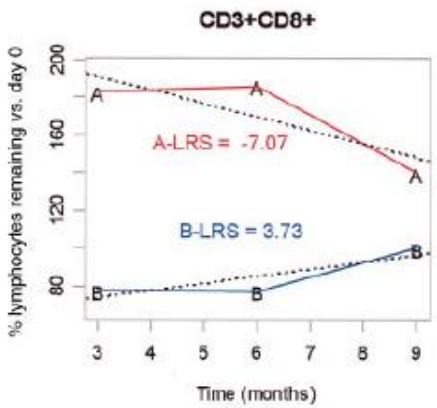
Baraut J Autoimmunity Review 2010

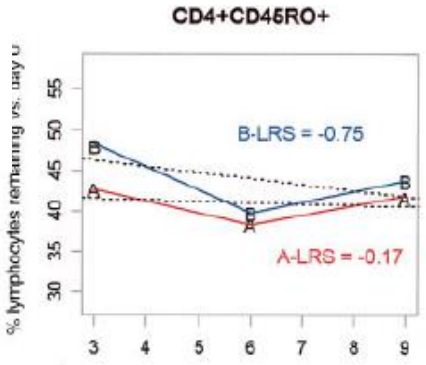
PATIENTS (n =14) : ns

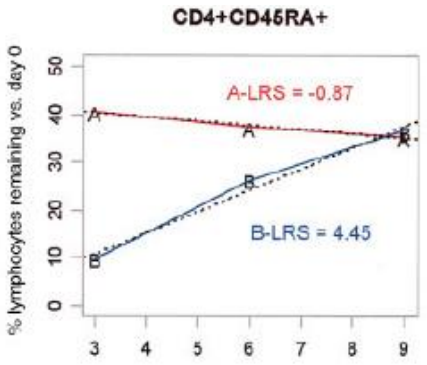
Rodnan : 17 ± 10 vs 43 ± 7, p < 0.03

SHAQ : 0.8 ± 0.7 vs 2.3 ± 0.2, p < 0.05

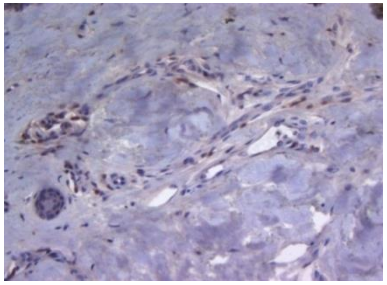




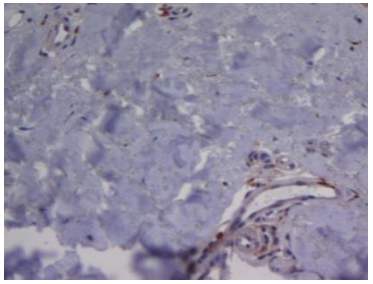




CD19+ et CD20+ et AC anti SCL70 (r = 0.27, p<0.05)
Lymphopenie T CD4+, CD4+CD45RA+: favorable SSc
TREC /CRP: rp< 0.001, TREC / CD19+: rp< O.OO1 (PR, SEP)



CD4 +



CD 25 +

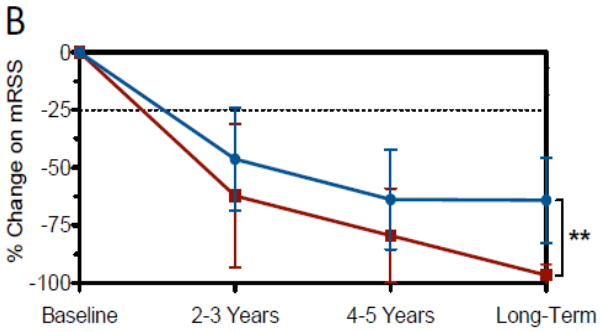
Barault 2013

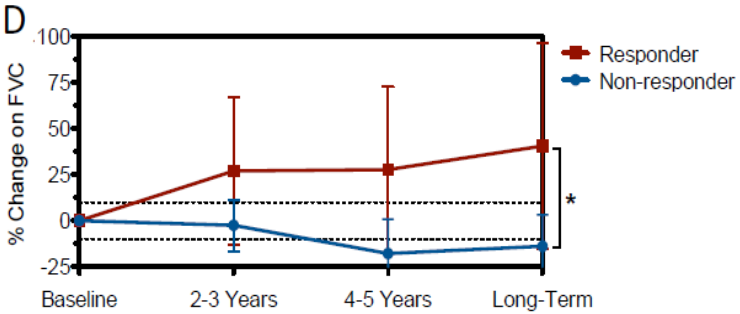
Farge D et al Arthr Rheum 2005

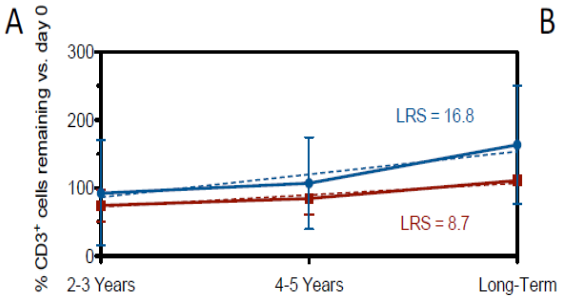
Long-term immune reconstitution and T-cell repertoire analysis after autologous HSCT in systemic sclerosis patients

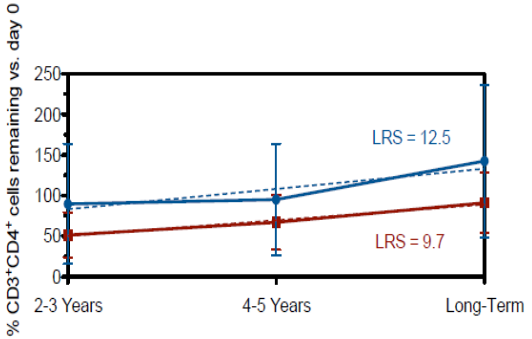
Farge et al. Journal of Hematology & Oncology (2017) 10:21

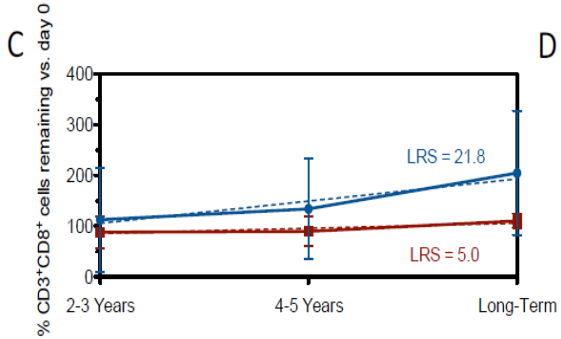
Long-term mRSS fall > 25% more pronounced in those improving FVC% > 10% (*P*=0.026
Pretransplant B cell clonal expansion + faster T-cells IR after aHSCT in non-responders /relapsing

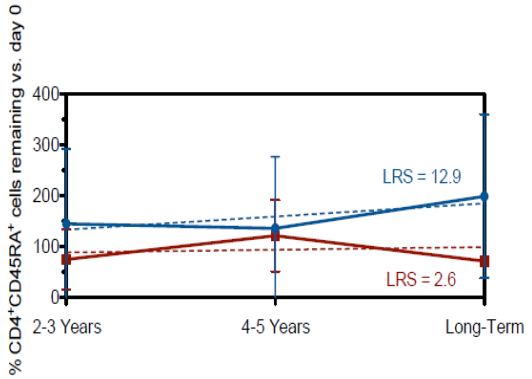


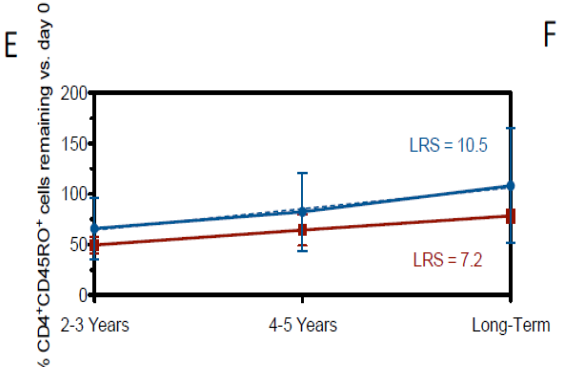


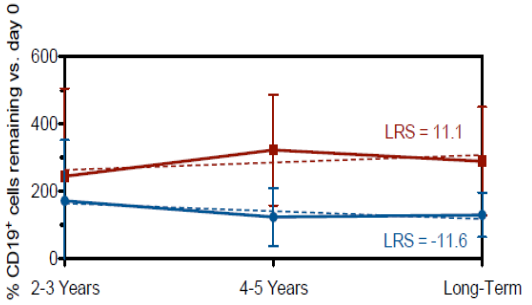












REGULAR ARTICLE

blood advances

Immune rebound associates with a favorable clinical response to autologous HSCT in systemic sclerosis patients

Lucas C. M. Arruda,[1,2] Kelen C. R. Malmegrim,[2,3] João R. Lima-Júnior,[2,4] Emmanuel Clave,[5,6] Juliana B. E. Dias,[7] Daniela A. Moraes,[7] Corinne Douay,[5] Isabelle Fournier,[5] Hélène Moins-Teisserenc,[5,6] Antônio José Alberdi,[6,8] Dimas T. Covas,[2,7] Belinda P. Simões,[2,7] Pauline Lansiaux,[9] Antoine Toubert,[5,6,*] and Maria Carolina Oliveira[1,2,7,*]

[1]Basic and Applied Immunology Program, Ribeirão Preto Medical School, [2]Center for Cell-based Therapy, Regional Hemotherapy Center of the Ribeirão Preto Medical School, [3]Department of Clinical, Toxicological and Bromatological Analysis, School of Pharmaceutical Sciences of Ribeirão Preto, and [4]Graduate Program on Bioscience Applied to Pharmacy, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; [5]INSERM Unité Mixte de Recherche 1160, Institut Universitaire d'Hématologie, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris (AP-HP), Paris, France; [6]Institut Universitaire d'Hématologie, Université Paris Diderot, Sorbonne Paris Cité, Paris, France; [7]Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; [8]Plateforme Technologique, Institut Universitaire d'Hématologie, Paris, France; and [9]Unité de Médecine Interne, Maladies Autoimmunes et Pathologie Vasculaire, UF 04, AP-HP, Centre de référence des maladies auto-immunes systèmiques rares d'Ile-de-France (site constitutif), FAI2R, Hôpital Saint-Louis, Paris, France

Submitted 27 July 2017; accepted 18 November 2017. DOI 10.1182/bloodadvances.2017011072.

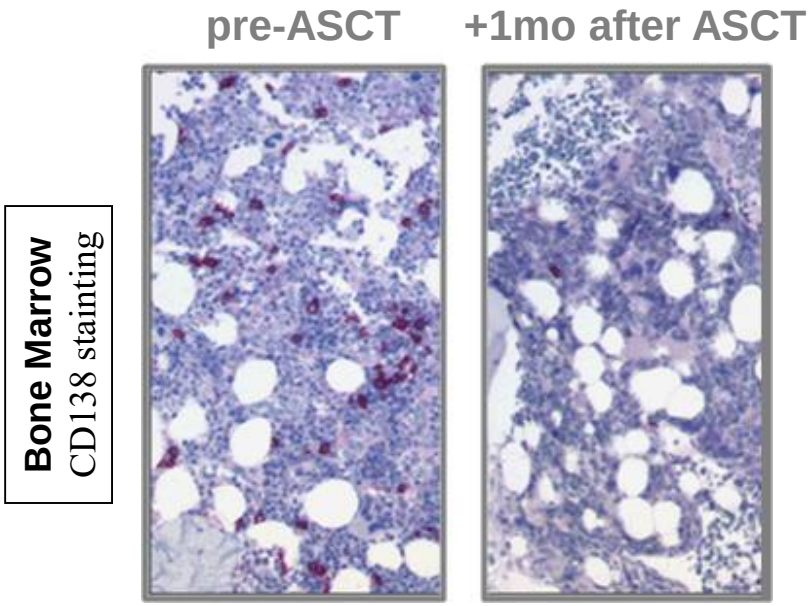
*A.T. and M.C.O. contributed equally to this study.

The data reported in this article have been deposited in the National Center for Biotechnology Information database (accession number SRP106516).

The full-text version of this article contains a data supplement.

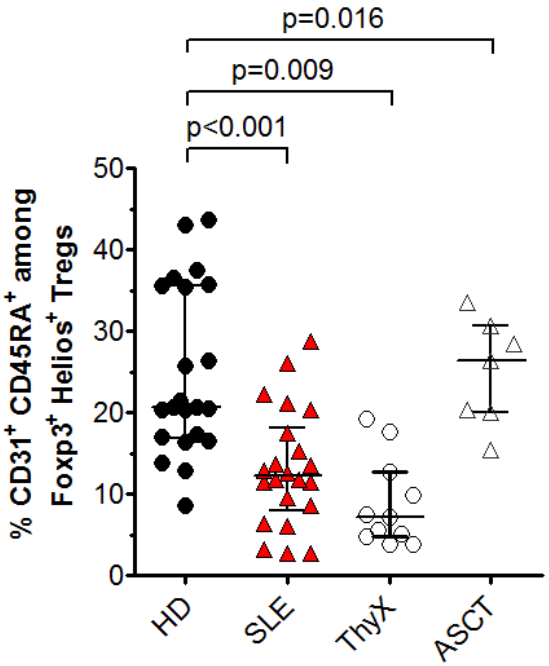
Clinical remissions after HSCT in SLE are associated with immune reset
eradication of autoreactive memory + profound reconfiguration of immune system

Plasma cell depletion with ATG



Alexander T et al., *Blood* 2009 (n =5 pts)

Recurrence of thymic-naive Tregs



Alexander T et al., *ARD* 2013

CHARITÉ

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

DFG Deutsche Forschungsgemeinschaft

Yes we can!

- **Reset tolerance and make it safer = (AREI) x 2**
- **Activity = > accreditation**
  - increased activity should not lower the quality
  - Patient selection and careful FU after HSCT
  - Respect of CI / follow GCP
- **Registration + research => new clinical studies**
  - ADWP registry + MED ADWP
  - Observational and translational research
- **Education + evaluation**
  - ADWP guidelines / meeting / national network
  - Rare orphan diseases plan
- **Innovation + implementation => fundings**
  - New regimen: conditioning /maintenance
  - Stem cell therapy before HSCT