

Traitement précoce des sclérodermies systémiques cutanées diffuses: place de l'autogreffe de cellules souches hématopoïétiques périphériques

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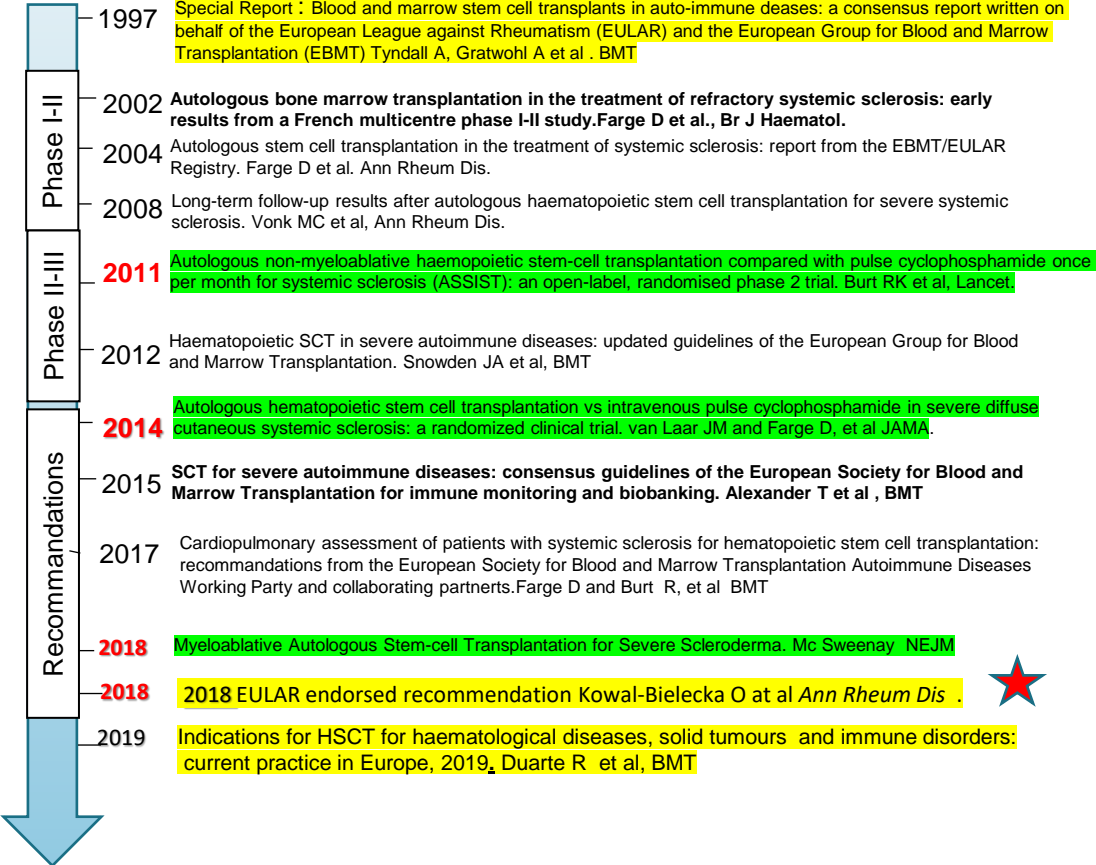
www.mathec.com

ADWP – Number of HSCT: 3947

EBMT Registry – August 2022

▶ MULTIPLE SCLEROSIS	2004	▶ HAEMATOLOGICAL	148
▶ CONNECTIVE TISSUE	985	ITP	39
SSc	799	AIHA	32
SLE	121	Evans'	24
PM-DM	18	<i>Other</i>	53
Sjogren	6	▶ VASCULITIS	67
Antiphosph. Syndrome	6	Granulomatosis with Polyangiitis (GPA)	12
<i>Other/Unknown</i>	35	Behcet's	17
▶ ARTHRITIS	205	Eosinophilic GPA	2
Rheumatoid arthritis	81	Polyarteritis	4
Juvenile chronic arthritis :		Takayasu	3
*Systemic JIA	72	<i>Other/Unknown</i>	29
*Articular JIA	21	▶ OTHER NEUROLOGICAL	143
*Other JIA	19	NMO	27
Psoriatic arthritis	3	CIDP	65
<i>Other</i>	9	Myasthenia gravis	10
▶ INFLAMMATORY BOWEL	283	<i>Other/Unknown</i>	41
Crohn's disease	232	▶ INSULIN DEPENDENT	20
Coeliac disease	18	DIABETES	
<i>Other</i>	33	▶ OTHER	8992

20 YEARS - 3 Randomized Control TRIALS : GRADE 1 evidence for AH SCT in SSC



Protocole National de Diagnostic et de Soins



Indications for AHSCT in early rapidly progressive SSc

**Age: 18 to 65 years + SSc diffuse/ limited with disease duration:
≤ 2 yrs + mRSS ≥ 20 and trunk involvement**

- ESR ≥ 25
- Hb < 11 without any other cause but SSc

≤ 5 years + mRSS ≥ 15 + Internal organ involvement

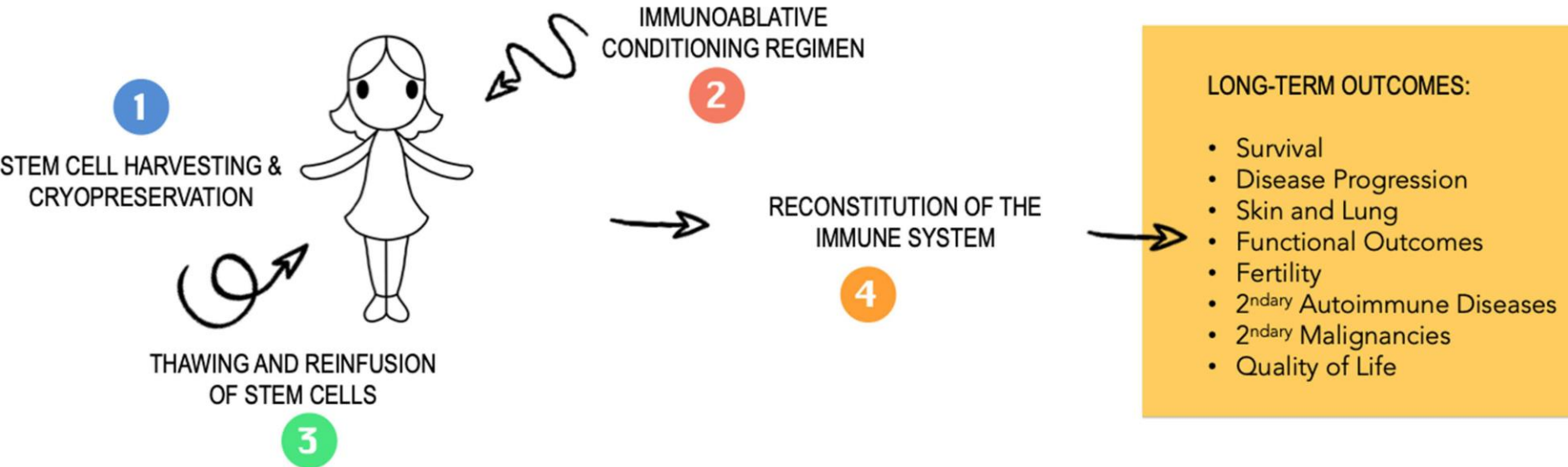
- Lung: FVC and / or DLCO ≤ 80% plus radiological interstitial disease
- Kidney : Hypertension, abnormal urinary sediment, altered renal function
- Heart : arrhythmia or conduction abnormalities

≤ 5 years disease duration + mRSS < 14 + progressive pulmonary disease

- Fall in FVC greater or equal 10 % and / or DLCO greater or equal to 15 %

Life after Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis

Moraes D, Oliveira MC
Journal of Blood Medicine 2021;12:951–964



Life after Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis

Moraes D, Oliveira MC *Journal of Blood Medicine* 2021;12 951–964

	Burt 2011 (ASSIST) 10 HSCT + 9 CY arm	van Laar, Farge 2014 (ASTIS) 79 HSCT + 77 CY arm	Sullivan 2018 (SCOT) 33 HSCT + 32 CY	Del Papa 2017 18 HSCT + 36 C
Age	45 y	43.8 y	45.9 y	41 y
Dis D	13.6 mo	16.8 mo	27 mo	24 mo
OS	100% both groups	80% vs 65% at 4 y	86% vs 51% at 6 y	89% vs 39% at 5 y
TRM	0%	10.6% (8/79)	3% (1/33)	5.6% (1/18)
PFS	100% vs 11% CY	77% vs 65% at 5.8 y	NA	NA
DIS PROG	0 vs 89% (8/9)	11% vs 35% at 5.8 y	18% vs 41% at 6	NA



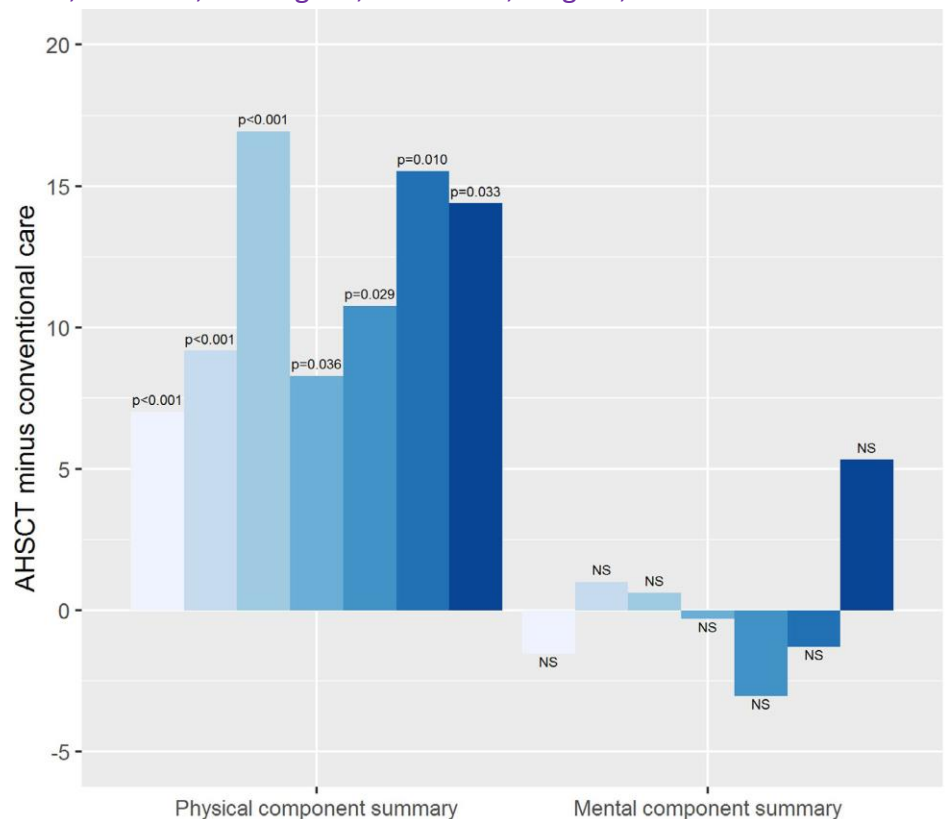
St Louis Hospital MATHEC before and 6 years after HSCT April 2018

Association of AHSCT in Systemic Sclerosis With Marked Improvement in Health-Related Quality of Life

Maltez N, Puyade M, Wang M, Lansiaux P, Marjanovic Z, Charles C, Steele R, Baron M, Colmegna I, Hudson M, Farge D; Canadian Scleroderma Research Group and the MATHEC-SFGMTC Network

Arthritis Rheumatol. 2021 Feb;73(2):305-314

	AHSCT (n = 41)	Conventional care (n = 65)
Age, yrs	44.7 ± 13.3	53.1 ± 10.7
Dis duration, yrs	2.6 ± 1.5	1.5 ± 1.0
MRSS (0–51)	25.0 ± 10.5	[27.5 ± 8.1
ILD, no. (%)	38 (92.7)	32 (49.2)
FVC, % pred	78.9 ± 17.5	83.4 ± 19.8
DLco, % pred	55.2 ± 15.5	62.2 ± 17.6
Previous renal crisis, no. (%)	0 [2]	14 (21.5)
Creatinine	111.2 ± 34.1	85.0 ± 46.7

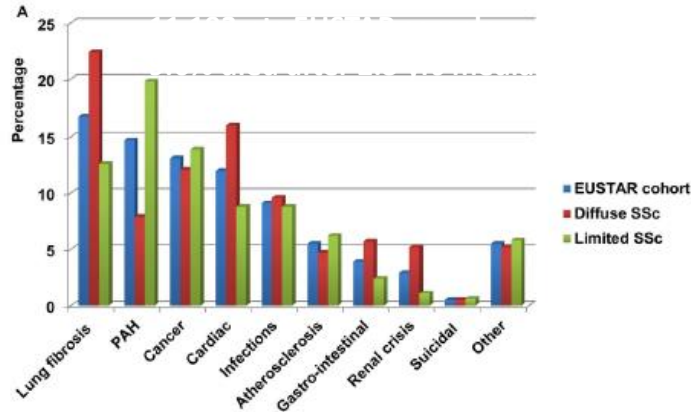


Change v1-v0 v2-v0 v3-v0 v4-v0 v5-v0 v6-v0 v7-v0

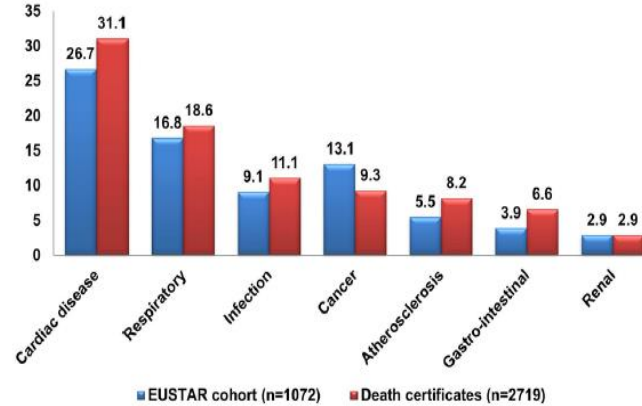
Mapping and predicting mortality from systemic sclerosis

(<http://dx.doi.org/10.1136/annrheumdis-2017-211448>).

Muriel Elhai,¹ Christophe Meune,² Marouane Boubaya,³ Jérôme Ayoub,¹



Primary heart disease: 30% of the deaths
 SMR : 1.03 (2000) to 0.6 (2011) per 105 men and women



2011 : EUSTAR cohort deaths + French death certificates

Subgroup	No. of studies	Cardiac involvement	No. of studies	Pulmonary interstitial involvement	No. of studies	PAH	No. of studies	Renal involvement
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Organ manifestation criteria

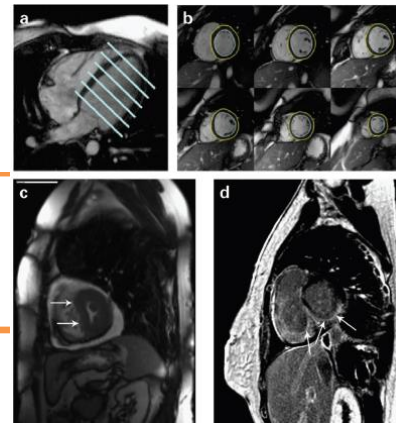
Standard	9	3.26 (2.3, 4.6)**	10	2.77 (2, 3.84)**	4	3.73 (1.67, 8.34)**	6	3.17 (2.16, 4.65)**
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Autologous stem cell transplantation in scleroderma

Dominique Farge^{1,2*}, Nassim Ait Abdallah¹, Zora Marjanovic³, Nicoletta Del Papa⁴

Presse Med 50 (2021)

Bone Marrow Transplantation (2017)



MULTIDISCIPLINARY MEETING (www.mathec.com):

- Evaluate indication,
- Search for absolute or transient contra-indication
- Evaluate potential risk factors for aHSCT treatment-related complications

EXCLUSION CRITERIA FOR aHSCT

APPROPRIATE CANDIDATE

**No indication
Or
Absolute contra-indication**

- Age >65 years.
- Respiratory failure, DLCO < 40%, FVC < 60%
- LVEF < 45% , severe coronary artery disease, untreated severe arrhythmia, cardiac tamponade, constrictive pericarditis.
- Renal failure (GFR < 40 ml/min)
- Active neoplasia or myelodysplasia..
- Acute or chronic uncontrolled infection.
- High risk of no compliance

Any cardiopulmonary risk factors *

Alternative conditioning regimens
using low doses CYC

No cardiopulmonary risk factors *

Standard conditioning regimens
200 mg/kg CYC total dose

*** Cardiopulmonary risk factors for aHSCT treatment-related complications**

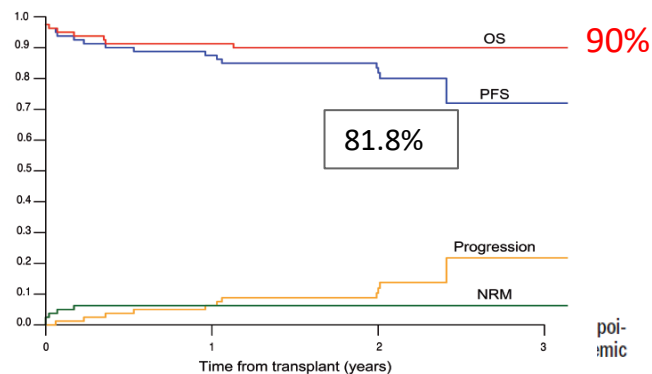
- Baseline (resting) PASP > 40 mmHg or mPAP > 25 mmHg, PASP > 45 mmHg or mPAP > 30 mmHg after fluid challenge Decrease or lack of augmentation of CO after fluid challenge
- Pulmonary vascular resistance > 3 Wood units
- D-sign of septal bounce on cardiac MRI

Patients	80
Age at aHSCT, years, median (range)	43 (20 - 62)
Sex, female	57 (71.3%)
Disease duration from SSc diagnosis, median (months)	23.8 (5.3-103.7)
Cardiac involvement	
Systolic blood pressure (mmHg) , median (range)	110 (76-145)
Diastolic blood pressure (mmHg) , median (range)	70 (40-90)
Heart rate, median (range)	82 (50-105)
Resting ECG, abnormal	4/80 (5%)
24h Holter ECG, abnormal	12/60 (20%)
Echocardiography, done	80 (100%)
LVEF (in %), median (range)	65% (47-84)
Pericardial effusion, present	5/79 (6.3%)
sPAP by cardiac echo (mmHg), median (range)	29 (8-59)
Cardiac MRI, done	59/80 (74%)
Cardiac MRI, abnormal**	11 (18.6%)
Right heart catheterization, done, median (range)	17/80 (21.3%)

Conditioning regimen	
CYC 200 mg/kg	72 (90.0%)
CYC other dose mg/kg	4 (5.0%)
CYC 100mg/kg + Thiotepa 10mg/kg	4 (5.0%)
Rabbit ATG, yes	80 (100%)
Thymoglobulin (Sanofi/Genzyme), mg/kg, median (range)	7.5 (2.5-7.5)
Grafalon (Neovi/Fresenius), mg/kg, median (range)	40 (30-41)

Previous immunosuppressive SSc medication, yes****	
Cyclophosphamide (i.v/oral)	48 (60%)
Dose (g), median (range)	6 (1-17)
Methotrexate	46 (58.2%)
Mycophenolate mofetil	16 (20.3%)
Prednisone or equivalent	64 (81.0%)
Azathioprine	8 (10.0%)
ATG rabbit	2 (2.5%)
Cyclosporine	3 (3.8%)

TRM = 6.25%



Post-transplant non-infectious complications in 21 (26%) patients Events (n=24)

CYC-related acute cardiomyopathy / 4 deaths	4
Cardiomyopathy with myocardial infarction	1
ARDS + acute heart failure	1
Arrhythmias	2
Pericardial effusion	1
Atrial flutter/or fibrillation	2
Allergy to ATG with respiratory failure + Pulmonary hemorrhagic syndrome	1
ATG-related fever	1
Acute pulmonary edema	1
Renal failure	3
Psychosis / depression	2
Epistaxis	1
Oral mucositis	1
Anal fissure	1
Hemorrhagic cystitis	2

Post-transplant infections reported in 60 (75%) patients Events (n=95)

Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: a pilot safety study that decreases neutropenic interval to 5 days

Richard K. Burt¹ · Xiaoqiang Han¹ · Kathleen Quigley¹ · Indira Annautovic¹ · Sanjiv J. Shah² · Daniel C. Lee² · Benjamin H. Freed² · Borko Jovanovic³ · Irene B. Helenowski³

Published online: 01 July 2020

Bone Marrow Transplantation
<https://doi.org/10.1038/s41409-020-0978-2>

Table 2 Transplantation inpatient and 1-year toxicity.

Parameter: where indicated includes mean/standard deviation (range)	All patients	Flu/Cy/ATG	Flu/Cy/ATG with rituximab ± IVIG	P value between regimens with and without rituximab
Transplant-related deaths	1/42	0/14	1/28	0.99
All deaths	4/42	2/14	2/18	0.99
Infections during inpatient hospitalization	0/42	0/14	0/28	NA
Day of discharge	10/1.3 (8–14)	9/1 (8–12)	10/1.3 (8–14)	0.03
Days absolute neutrophil count <500/uL	5.2/2.2 (1–10)	4.4/2 (1–8)	5.6/2.2 (2–10)	0.07
Number PRBC transfusion	1.85/2 (0–9)	1.64/1.3 (0–4)	1.96/2.3 (0–9)	0.90
Number Platelet transfusions	0.3/0.97 (0–5)	0.07/0.3 (0–1)	0.46/1.2 (0–5)	0.31
Number of patients with fever (>38.0 °C)	10/42	4/14	6/28	0.71
Upper respiratory tract infections (sinusitis, bronchitis, bacterial pneumonia)	5/42	4/14 3 restart MMF	1/28	0.04
Viral (BK uremia, influenza)	2/42	0/14	2/28	0.54
Number of secondary autoimmune diseases (hypothyroidism (2), rheumatoid arthritis (1))	3/42	3/14	0/28	0.03

TRM : 2.4 %

= > CONDITIONING LESS TOXIC:

CYCLO 60 mg/kg x 1

+ Fludarabine 30mg/m² x 3

⇒ RATG at least 12 h iv

**0.5 mg/Kg/D at D-5, 1 mg/Kg/D-4 ,
1.5 mg/kg D-3 to**

=> steroids 1 mg/Kg/ D-5 to D-1

Table 3 Outcome after transplantation between regimens with and without rituximab.

Parameter	Flu/Cy/ATG mean/SD (range)	Flu/Cy/ATG rituximab ± IVIG Mean/SD (range)	P value between regimens with and without rituximab
Relapse at 1 year	5/14 (36%)	1/28 (4%)	0.01
Overall survival at 1 year	12/14 (86%)	27/28 (96.4%)	0.25
mRSS pre-HSCT	17.8/9.9 (5–36)	17.9/13 (3–48)	
mRSS change at 12 months	6.1/3.6 (1–13)	8.5/10.1 (0–34)	
mRSS net change after 1 year	-11.7 ^a	-9.4 ^b	0.28
FVC pre-HSCT (percent predicted)	56.3/16.1 (32–94)	65.8/15.6 (41–95)	
FVC at 6 months	62.3/13.3 (41–86)	69.6/17.5 (42–98)	

RITUXIMAB

Clinical responses ?

Lower relapse rates

Secondary auto-immune diseases

WHO IS CANDIDATE FOR HSCT in SSc and HOW TO PROCEED in 2022 ?

1. PATIENT with early organ involvement with disease progression : a potential candidate

2. PATIENT SELECTION +++

Not too early ..but not too late before 5 years disease duration

Early detection of internal organ involvement

Rule out any contra-indication

MATHEC

<https://www.mathec.com/soignants/rcp-mathec/>

3. MATHEC multidisciplinary experts online evaluation

A horizontal navigation bar with a dark blue background and white text. It contains a home icon followed by the text "A PROPOS DE MATHEC", "SOIGNANTS", "PATIENTS", "RECHERCHE", "LIENS", "CONTACT", and "LOGIN", each with a small downward arrow.

4. BONE MARROW TRANSPLANT CENTER : EXPERT CENTER ACCREDITED FOR ALLOGENEIC BONE MARROW TRANSPLANTATION

5 . MOBILISATION and CONDITIONNING: towards lower toxicity

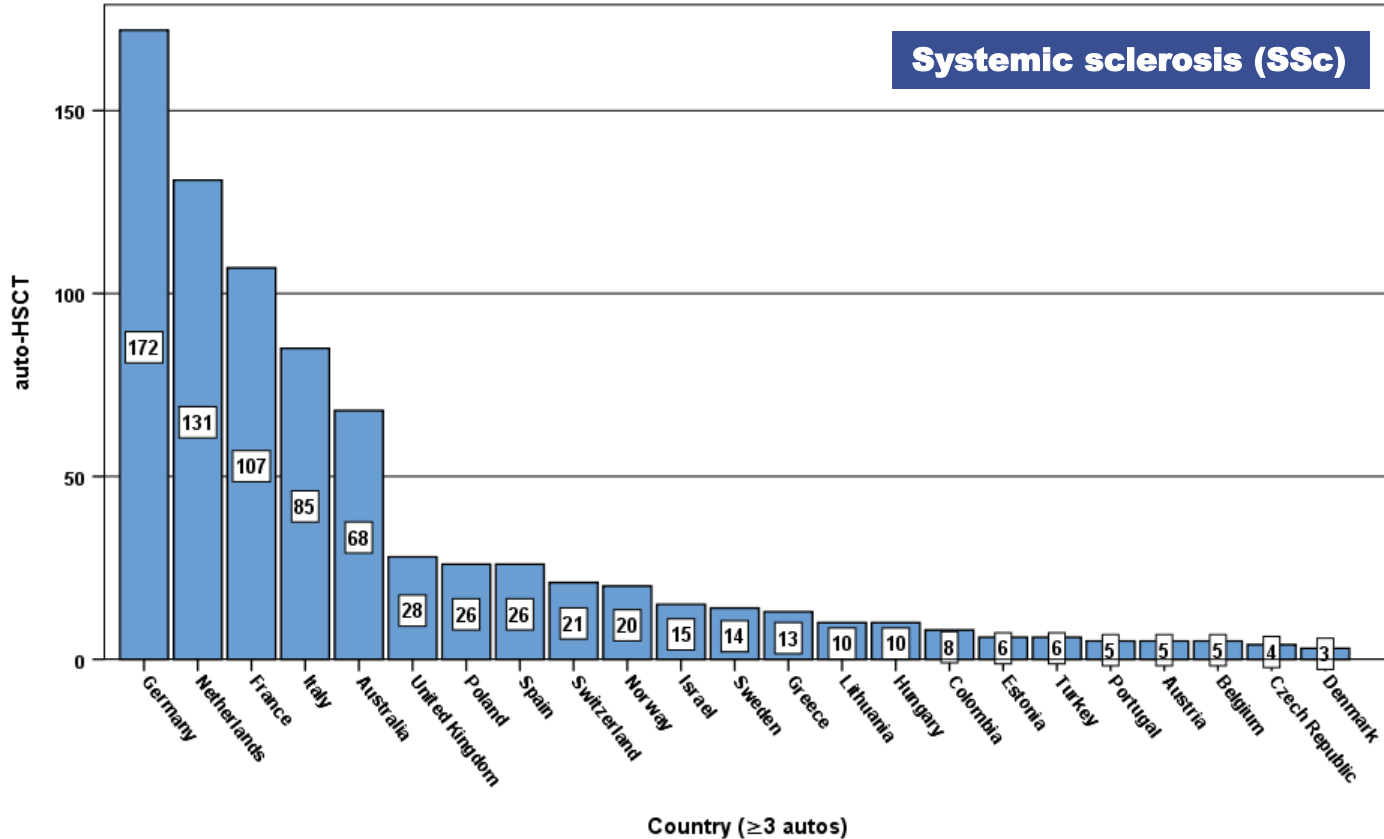
6. Good Clinical Practice Guidelines : JACIE accredited center

centre de référence
maladies rares

The logo for "fair" (French acronym for "Association Française des Maladies Rares"). It features a stylized DNA double helix in red and blue above the text "fair" in a bold, sans-serif font. The "i" and "a" are connected, and the "r" has a small cluster of colorful dots above it.

Systemic Sclerosis

Auto / country – 1994-2022 (n = 798) – August 2022

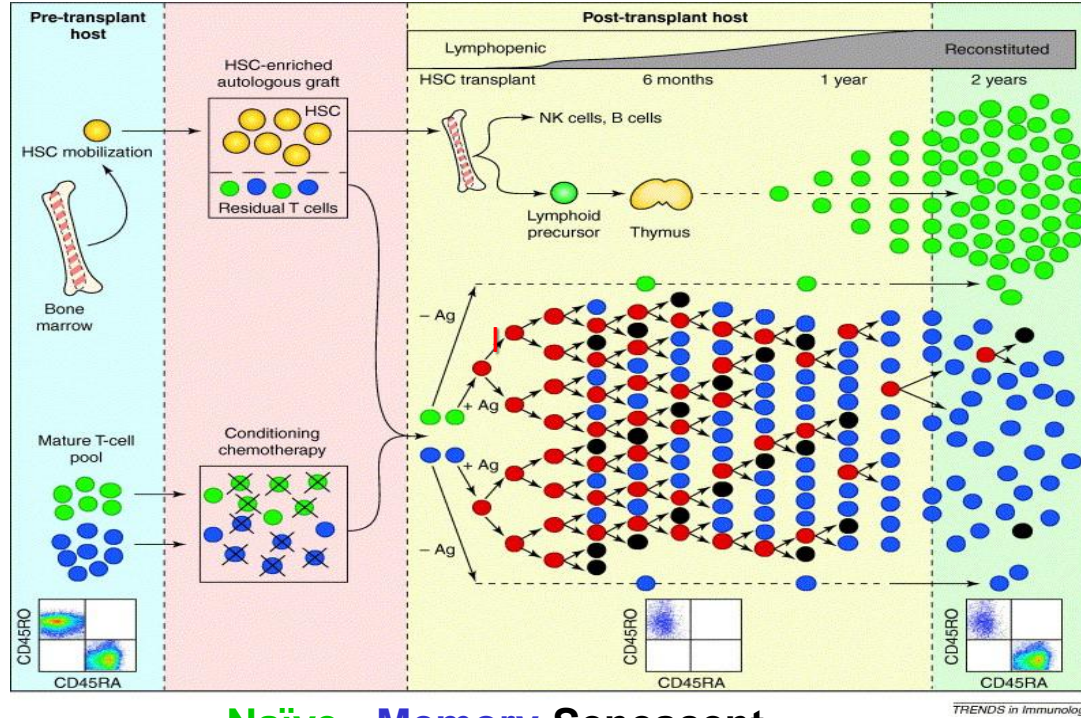


Immune reconstitution after AHSCT: renewal of the immune repertoire

Type I : replacement of mature T/B memory repertoire with naïve, non-pathogenic cells

Type II : reinstatement of Immune Regulation ↑ nb and/or function of regulatory cells

immunophenotyping, TREC (Thymic output), CDR3 spectratyping / nucleotide sequencing



Naïve Memory Senescent

TRENDS in Immunology

Farge Arthritis Rhum 2008 (n = 7), Barault BMT2013 (n = 7),

Michel BMT 2016 (n=7), Farge Hemato Oncol 2017 (n=12),

Arruda Blood Advances 2018 (n=31)

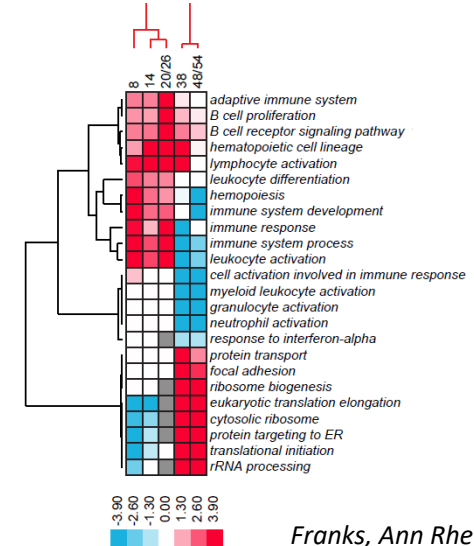
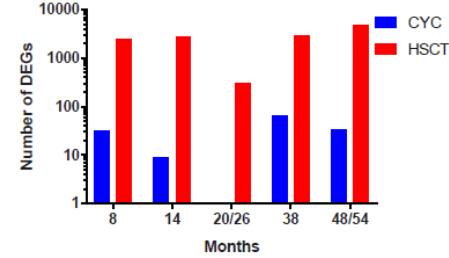
↑ T regulatory cells Foxp3

↑ naïve B cells after HSCT

↑ CD4⁺CD25^{high}FoxP3 ↑regulatory T cell

↑ CD8⁺FoxP3 ↑ suppressive function

Differential gene expression analysis



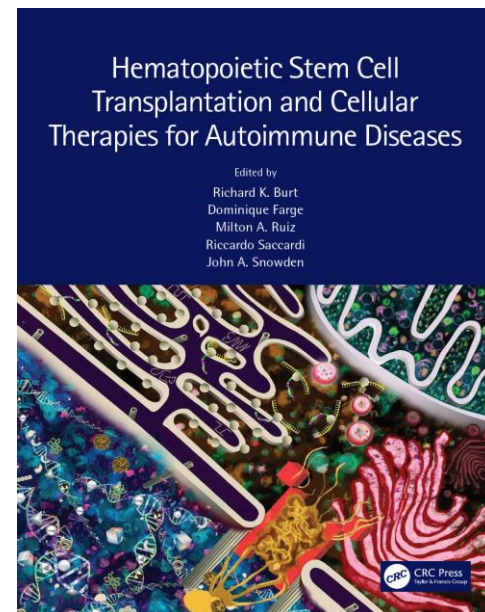
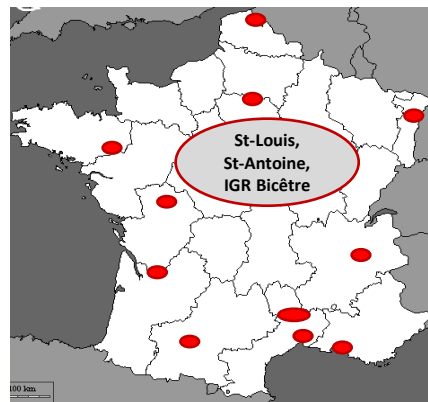
Franks, Ann Rheum Dis 2020



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Mathec – Maladies Auto-immunes et Thérapie Cellulaire



Hematopoietic Stem Cell Transplantation and Cellular Therapies for Autoimmune Diseases

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NTIC
Multidisciplinary
Common procedures,
Evaluation
Indication,
Follow-up
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<https://doi.org/10.1201/9781315151366>