Disease Status evaluation for Autoimmune Diseases

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Autoimmune Diseases

- family of more than 100 heterogeneous diseases, which affect 5 to 8% of the population worldwide

- characterised by aberrant activation of the immune system with failure of immune regulation to maintain adapted tolerance

- most patients can be treated with drugs suppressing the immune mediated inflammation, but when these fail or are too toxic, alternative strategies are needed

- severe forms of systemic ADs, such as multiple sclerosis (MS), systemic sclerosis (SSc), lupus erythematosis (SLE), Crohn’s disease, … could be difficult to treat
HSCT for ADs: EBMT Registry

September 2012 *
*All transplants not yet registered for 2012

- Transplant procedures: 1440
- Patients: 1400
- Male/Female %: 39/61
- Centres /Countries: 223/32
- Overall Follow up: 2.9y (<1-24)

<table>
<thead>
<tr>
<th></th>
<th>Autografts n=1329</th>
<th>Allografts n=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1324</td>
<td>75</td>
</tr>
<tr>
<td>Second</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Third</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Median age at 1st transplant</td>
<td>36y (3-76)</td>
<td>14y (&lt;1-69)</td>
</tr>
</tbody>
</table>
Number of HSCT: 1440- EBMT Registry

September 2012 *

*All transplants not yet registered for 2012

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>504</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>448</td>
</tr>
<tr>
<td>SSc</td>
<td>300</td>
</tr>
<tr>
<td>SLE</td>
<td>103</td>
</tr>
<tr>
<td>PM-DM</td>
<td>20</td>
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<tr>
<td>Sjogren</td>
<td>3</td>
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<tr>
<td>Antiphosph. syndrome</td>
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<tr>
<td>Other/Unknown</td>
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<tr>
<td>Arthritis</td>
<td>173</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>88</td>
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<tr>
<td>Juvenile chronic arthritis</td>
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<tr>
<td>- Systemic JIA</td>
<td>50</td>
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<tr>
<td>- Other JIA</td>
<td>18</td>
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<tr>
<td>- Polyarticular JIA</td>
<td>10</td>
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<tr>
<td>Psoriatic arthritis</td>
<td>3</td>
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<tr>
<td>Other</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>107</td>
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<tr>
<td>Crohn's disease</td>
<td>95</td>
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<tr>
<td>Ulcerative colitis</td>
<td>4</td>
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<tr>
<td>Other</td>
<td>7</td>
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<tr>
<td>Haematological</td>
<td>81</td>
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<tr>
<td>ITP</td>
<td>25</td>
</tr>
<tr>
<td>Evans'</td>
<td>19</td>
</tr>
<tr>
<td>AIHA</td>
<td>19</td>
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<tr>
<td>Other</td>
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<tr>
<td>Vasculitis</td>
<td>43</td>
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<tr>
<td>Wegener's</td>
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<td>Behcet's</td>
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<td>Takayasu</td>
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<tr>
<td>Microscopic poly. nodosa</td>
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<td>Classical poly. nodosa</td>
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<td>Churg-Strauss</td>
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<tr>
<td>Other/Unknown</td>
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<tr>
<td>Other neurological</td>
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<tr>
<td>Myasthenia gravis</td>
<td>5</td>
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<tr>
<td>Other/Unknown</td>
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<tr>
<td>Insulin dependent diabetes</td>
<td>10</td>
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<tr>
<td>Other/Unknown/missing</td>
<td>31</td>
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</tbody>
</table>
Disease Breakdown 1999 / 2004-2005

**Transplants in 1999**
- RA: 28%
- MS: 25%
- JCA: 9%
- Unknown: 2%
- Vasculitis: 1%
- Wegener: 2%
- AIHA: 3%
- PM_DM: 3%
- SLE: 9%
- SSc: 7%
- ITP: 2%
- IBD: 1%

**Transplants in 2004-2005**
- MS: 37%
- Wegener: 1%
- ITP: 2%
- IBD: 2%
- JCA: 2%
- RA: 2%
- Vasculitis: 3%
- Evan's: 3%
- SLE: 9%
- SSc: 24%
- Unknown: 7%
SCLERODERMA σκλερος + δερμα
SCLERODERMA

- Scleroderma is a rare, chronic autoimmune disease characterized by excessive deposits of collagen in the skin or other organs.

- The primary finding in scleroderma is thickening and tightening of the skin.

- It is four times as common in women than in men.
Raynaud's phenomenon may precede scleroderma by several years

Raynaud's phenomenon is due to vasoconstriction of the small arteries of exposed peripheries - particularly the hands and feet - in the cold.

It is classically characterised by a triphasic colour change - first white, then blue and finally red on rewarming.
TWO broad categories:

“localized scleroderma” *(not to be confused with limited)* which indicates distinct skin lesions

“systemic sclerosis” which indicates similar skin symptoms and the potential for internal organ disease; the terms *limited and diffuse* refer to the extent of skin involvement.
The limited form is much milder:

- slow onset and progression,
- skin hardening is usually confined to the hands and face
- internal organ involvement is less severe
- much better prognosis is expected
The **limited form** is often referred to as **CREST syndrome**

"**CREST**" is an acronym for the five main features:

**Calcinosi**s (deposition of calcium in lumps under the skin)

**Raynaud’s syndrome** (vasospastic disorder causing discoloration of the fingers, toes, and occasionally other areas)

**Esophageal dysmotility**

**Sclerodactyly** (localized thickening and tightness of the skin of the fingers)

**Telangiectas**ia (small dilated blood vessels near the surface of the skin or mucous)
Diffuse scleroderma or systemic sclerosis, the generalized type of the disease:

- can be fatal as a result of heart, kidney, lung or intestinal damage

- in diffuse disease the skin changes can affect the whole body

- tightening of the skin around the fingers, the face and other areas of the body causing contractures (fixed joints) and a small mouth (microstomia), ulceration, dryness and irritation, broken blood vessels (telangiectasia) on the face and hands and calcinosis protruding through the skin
Systemic Sclerosis

MODIFIED RODNAN SKIN SCORE

0 Uninvolved
1 Mild thickening
2 Moderate thickening
3 Severe thickening

- Upper arm
- Face
- Upper arm
- Anterior chest
- Forearm
- Hand
- Hand
- Fingers
- Fingers
- Thigh
- Thigh
- Leg
- Leg
- Foot
- Foot

Total Skin Score: ........................................

Image: Examples of skin changes in systemic sclerosis.
Joints destructions in patient with Scleroderma
The internal organs can be affected in both limited and diffuse disease.

Heart and lung involvement can also be associated with both forms, although the heart is not as commonly affected as the lung.

Lung fibrosis is more common in diffuse patients.

A small percentage (15%) of patients with limited form will develop pulmonary hypertension (PHT), a condition affecting the vessels taking blood from the right side of the heart to the lungs.

The kidneys are rarely affected in limited disease, however approximately 5% - 10% of diffuse patients will incur some form of renal involvement.
Lung involvement in Scleroderma
Right ventricular hypertrophy due to pulmonary fibrosis in Scleroderma
Gastrointestinal System Related Symptoms

peptic stricture, or narrowing of the esophagus near the junction with the stomach due to chronic gastroesophageal reflux, the most common cause of dysphagia, or difficulty swallowing, in scleroderma

barium graphy: lower esophageal sphincter involvement small intestine and colon involvements
<table>
<thead>
<tr>
<th>Organ</th>
<th>INVOLVEMENT</th>
<th>EXAMINATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>Scleroderma, necrosis</td>
<td>Rodnan,</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>Gastroesophageal reflux, telangiectasies, constipation/diarrhea, malabsorption, fecal incontinence</td>
<td>ENDOSCOPY, Blood cell count, ferritin, serum electrophoresis</td>
</tr>
<tr>
<td>LUNG</td>
<td>Alvéolitis, fibrosis</td>
<td>X RAY, LUNG FUNCTION TEST, WALKING TEST BLOOD GAZ, CT SCANN</td>
</tr>
<tr>
<td>PULMONARY VESSELS</td>
<td>Pulmonary hypertension ++++</td>
<td>Echocardiopgraphy, VIT LVEF right catheter if PHT</td>
</tr>
<tr>
<td>HEART</td>
<td>fibrosis, conduction /rythm disturbances, necrosis, CY tox</td>
<td>EKG, 24 hr Holter EKG, Echocardiography</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>HYPERTENSION, RENAL CRISIS, incontinend</td>
<td>BP + Pulse, serum Creatinin, Urinary sediment and 24 hr Protenuria</td>
</tr>
<tr>
<td>Neurologicla and psyhiatric</td>
<td>Anxio-depression</td>
<td>Mental Status</td>
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<tr>
<td>Mucosal</td>
<td>Dryness, sclerosis</td>
<td>OPH, dental, gynecological</td>
</tr>
<tr>
<td>Genital</td>
<td>Sclerosis, impotency</td>
<td>Clinical examination</td>
</tr>
</tbody>
</table>
SURVIVAL ACCORDING TO VISCERAL INVOLVEMENT

Arthritis and Rhumatism, Altman 1991

Arthritis and Rhumatism, Steen 2000
### AUTOIMMUNE DISORDERS – I (main disease code 10)

**Classification**
- Connective Tissue Disease

- Systemic sclerosis (SS)

**Date of this HSCT:** ......... - ......... - .........

#### Involvement/Clinical problem
- Diffuse cutaneous
- Limited cutaneous
- Lung parenchyma
- Pulmonary hypertension
- Systemic hypertension
- Renal (biopsy type: ______)
- Oesophagus
- Other GI tract
- Raynaud
- CREST
- Other, specify: ______

#### Presence

- No
- Yes

#### Indication for HSCT

- No
- Yes

**Antibodies studied**

- No

- Yes: Scl 70 positive
  - ACA positive

- Normal/Negative
- Elevated/Positive
- Not evaluated
# STATUS OF DISEASE AT HSCT

*Evaluation should be performed <2 weeks prior to conditioning*

## DISEASE STATUS
- [ ] Limited (cutaneous thickening distal to elbows or knees, but not proximal)
- [ ] Diffuse
- [ ] Other

## SKIN THICKNESS
*Modified Rodnan Skin Score (max 51)*: ________________  
☐ Not evaluated  ☐ Unknown  
*(Appendix B. 10)*

## LABORATORY VALUES

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<tr>
<td>Serum creatinine</td>
<td>(µmol/l)</td>
<td>☐ Not evaluated</td>
<td>☐ unknown</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>(ml/min)</td>
<td>☐ Not evaluated</td>
<td>☐ unknown</td>
</tr>
<tr>
<td>Creatinine phosphokinase</td>
<td>(IU/l)</td>
<td>☐ Not evaluated</td>
<td>☐ unknown</td>
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</tbody>
</table>

Proteinuria:  [ ] Absent  [ ] Present  ☐ Not evaluated  ☐ Unknown

## AUTOANTIBODIES
Were tests for autoantibodies done at conditioning?  [ ] No  [ ] Yes  [ ] Unknown

**Specify antibody:**
- Anti-DNA topoisomerase I (Scl-70):  ☐ Negative  ☐ Positive  ☐ Not evaluated  ☐ unknown
- Anti-centromere (ACA):  ☐ Negative  ☐ Positive  ☐ Not evaluated  ☐ unknown
- Anti-nuclear (ANA):  ☐ Negative  ☐ Positive  ☐ Not evaluated  ☐ unknown
- Other, specify: ________________  ☐ Negative  ☐ Positive

## PHYSICAL EXAMINATION RESULTS

<table>
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<tr>
<th></th>
<th>☐ No</th>
<th>☐ Yes</th>
<th>☐ Not evaluated</th>
<th>☐ Unknown</th>
</tr>
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<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>☐</td>
<td>☐</td>
<td>☐ Not evaluated</td>
<td>☐ Unknown</td>
</tr>
<tr>
<td>DLCO</td>
<td>☐</td>
<td>☐</td>
<td>☐ Not evaluated</td>
<td>☐ Unknown</td>
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<tr>
<td>Restrictive pulmonary function pattern</td>
<td>☐ No</td>
<td>☐ Yes</td>
<td>☐ Not evaluated</td>
<td>☐ Unknown</td>
</tr>
<tr>
<td>Fibrosis on CXR</td>
<td>☐ No</td>
<td>☐ Yes</td>
<td>☐ Not evaluated</td>
<td>☐ Unknown</td>
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<tr>
<td>Pulmonary artery hypertension (ECHO)</td>
<td>☐ No</td>
<td>☐ Yes</td>
<td>☐ Not evaluated</td>
<td>☐ Unknown</td>
</tr>
<tr>
<td>Mean PAP: mm/Hg</td>
<td>☐</td>
<td>☐</td>
<td>☐ Not evaluated</td>
<td>☐ Unknown</td>
</tr>
</tbody>
</table>

| Systemic hypertension requiring treatment | ☐ No | ☐ Yes: ☐ With ACE Inhibitor ☐ With other, specify: ________________  | ☐ Not evaluated | ☐ Unknown |
| Arrhythmia / conduction blocks | ☐ No | ☐ Yes | ☐ Not evaluated | ☐ Unknown |
SCC Treatment

- Current therapies use medications that focus on the four main features of the disease:
  - **Inflammation** (NSAIDs or corticosteroids)
  - **Autoimmunity** (methotrexate, cyclosporine, antithymocyte globulin, mycophenolate mofetil and cyclophosphamide)
  - **Vascular disease** (calcium channel blockers, bosentan, prostacyclin, or nitric oxide)
  - **Tissue fibrosis** (colchicine, para-aminobenzoic acid (PABA), dimethyl sulfoxide, and D-penicillamine)
DISEASE SPECIFIC RECOMMENDATIONS e.g. SSc

- HSCT can be considered as treatment for selected patients with early SSc

- Patients to be considered for HSCT include those with diffuse SSc with disease duration years since development of first non-Raynaud’s symptoms with a modified Rodnan skin score \( \geq 15 \) plus major organ involvement (with documented evidence of onset or clinically significant worsening in the previous 6 months) as defined by at least one of:

  (a) respiratory involvement with a DLCO and/or FVC \(< 70\%\) of predicted and evidence of interstitial lung disease (chest X-ray and/or HR-CT scan)

  (b) cardiac involvement with conduction disturbances, including second-/third-degree atrioventricular block, intra-ventricular conduction disturbance, left axis deviation, atrial or ventricular rhythm disturbance, pericarditis \(< 1\) cm on cardiac ultrasound

  (c) renal involvement with proteinuria \( > 0.3\) g/24h, not explained by other causes than systemic sclerosis
DEFINITIONS IN SSC

• **Baseline = last assessment before mobilization (max 3 months)**

  - Heart: LVEF < 30% by MUGA (or cardiac echo)
  - Lungs: respiratory failure = resting PaO$_2$ < 8 kPa (< 60 mmHg) *and/or oxygen dependency* resting PaCO$_2$ > 6.7 kPa (> 50 mmHg) without O2 supply
  - Kidney: need for renal replacement therapy

When major organ failure has occurred, its persistence is to be confirmed by repeated evaluation after 3 months.

• **Progression : any of the following changes from baseline:**

  - ≥ 10% drop in (F)VC and/or ≥ 15% drop in DLCO (of predicted values), ≥ 15% drop in LVEF by echo or MUGA, ≥ 15% drop in body weight, ≥ 30% drop in creatinine clearance, ≥ 30% increase in modified Rodnan skin score (mRSS); ≥ 0.5 increase in SHAQ.
Multiple Sclerosis
-In multiple sclerosis, an agent such as a virus or foreign antigen, *in theory*, may alter or interact with the immune system so that the immune system perceives myelin as an intruder and attacks it.

-Inflammation occurs and causes myelin to disappear. Consequently, the electrical impulses that travel along the nerves decelerate, that is, become slower.

-In addition, the nerves themselves are damaged. While some of the myelin may be repaired after the assault, some of the nerves are stripped of their myelin covering (become demyelinated).

-Scarring also occurs, and material is deposited into the scars and forms plaques. As more and more nerves are affected, a person experiences a progressive interference with functions that are controlled by the nervous system such as vision, speech, walking, writing, and memory.
Monitoring inflammatory activity in MS

Inflammation and demyelination

MRI

T1 + Gad

T2
# INITIAL DIAGNOSIS

Has the information requested in this section been submitted with a previous HSCT registration?

- [ ] Yes: proceed to “Date of HSCT” on page 4
- [ ] No: proceed with this section

## DIAGNOSTIC CRITERIA

Did the patient meet the Poser criteria for clinically-definite Multiple Sclerosis?

(Two attacks and clinical evidence of two separate lesions OR Two attacks; clinical evidence of one lesion and paraclinical evidence of another, separate lesion)

- [ ] No
- [ ] Yes
- [ ] Unknown

Did the patient meet the criteria for laboratory-supported Multiple Sclerosis?

- [ ] No
- [ ] Yes
- [ ] Unknown
The Poser criteria are:

**Clinically definite MS:**
- 2 attacks and clinical evidence of 2 separate lesions
- 2 attacks, clinical evidence of one and paraclinical evidence of another separate lesion

**Laboratory supported Definite MS:**
- 2 attacks, either clinical or paraclinical evidence of 1 lesion, and cerebrospinal fluid immunologic abnormalities
- 1 attack, clinical evidence of 2 separate lesions & CSF abnormalities
- 1 attack, clinical evidence of 1 and paraclinical evidence of another separate lesion, and CSF abnormalities

**Clinically probable MS:**
- 2 attacks and clinical evidence of 1 lesion
- 1 attack and clinical evidence of 2 separate lesions
- 1 attack, clinical evidence of 1 lesion, and paraclinical evidence of another separate lesion

**Laboratory supported probable MS:**
- 2 attacks and CSF abnormalities
STATUS OF DISEASE AT HSCT

Evaluation should be performed less than 2 weeks prior to conditioning

DISEASE COURSE
Indicate the disease course between diagnosis and mobilisation/HSCT

☐ Progressive relapsing (malignant)
☐ Primary progressive
☐ Secondary progressive (may have had previous Relapsing/Remitting)
☐ Relapsing/Remitting
☐ Not evaluable, explain: _______________________________________

Did the patient progress during the 2-years prior to mobilisation/HSCT?
☐ No
☐ Yes, number of relapses/progressions.........................
☐ Unknown
**CLINICAL EVALUATION**

**Scripps neurological rating scale**
Score: ........................................

☐ Unknown    ☐ Not evaluated

**Kurtze functional systems**
Overall score: ........................................

☐ Unknown    ☐ Not evaluated

**Kurtze Expanded Disability Status**
Scale (EDSS): ........................................

☐ Unknown    ☐ Not evaluated

**Composite Scale**
Score: ........................................

☐ Unknown    ☐ Not evaluated
Kurtzke’s EDSS scores 8 functional systems from 0 for normal to 5 or 6 for maximal impairment. Based on these functional system scores and the person’s ability to walk, the EDSS is determined.

The EDSS goes in half point scores from 0.0 for normal to 10.0 for dead from MS. From 0.0-4.0, people are able to walk without assistance, and the EDSS is derived from the functional system scores.

From 4.0-7.5, the EDSS score comes mainly from how far the person can walk and with what assistance. Essentially, point 6 on the scale represents walking with a cane, and this point is often used as an endpoint in studies looking at progression of disability.

From 7.5-10.0, the main determinant of EDSS is the person’s ability to transfer from wheelchair to bed and to self-care.

The disability rating scale is based upon neurological testing and examination, looking for abnormalities in functional systems.

The EDSS in detail is laid out below, in relation to the functional systems it affects; the functional systems are: pyramidal (motor functions like walking), cerebellar (coordination), brain stem (speech and swallowing), sensory (touch, vibration and pain), bowel and bladder functions, visual, mental, and any other (includes any other neurological findings due to MS).
Kurtzke Functional Systems Scores (FSS)

Pyramidal Functions
0 - Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)

Cerebellar Functions
0 - Normal
1 - Abnormal signs without disability
2 - Mild ataxia (tremor or clumsy movements easily seen, minor interference with function)
3 - Moderate truncal or limb ataxia (tremor or clumsy movements interfere with function in all spheres)
4 - Severe ataxia in all limbs (most function is very difficult)
5 - Unable to perform coordinated movements due to ataxia
9 - (Unknown)

Record #1 in small box when weakness (grade 3 or worse on pyramidal) interferes with testing.

Bowel and Bladder Function
(Rate on the basis of the worse function, either bowel or bladder)
0 - Normal
1 - Mild urinary hesitance, urgency, or retention
2 - Moderate hesitance, urgency, retention of bowel or bladder, or rare urinary incontinence (intermittent self-catheterization, manual compression to evacuate bladder, or finger evacuation of stool)
3 - Frequent urinary incontinence
4 - In need of almost constant catheterization (and constant use of measures to evacuate stool)
5 - Loss of bladder function
6 - Loss of bowel and bladder function
9 - (Unknown)

Visual Function
0 - Normal
1 - Scotoma with visual acuity (corrected) better than 20/30
2 - Worse eye with scotoma with maximal visual acuity (corrected) of 20/30–20/59
3 - Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60–20/99
4 - Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100–20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5 - Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6 - Grade 5 plus maximal visual acuity of better eye of 20/60 or less
9 - (Unknown)

Record #1 in small box for presence of temporal pallor

Cerebral (or Mental) Functions
0 - Normal
1 - Mood alteration only (does not affect EDSS score)
2 - Mild decrease in mentation
3 - Moderate decrease in mentation
4 - Marked decrease in mentation (chronic brain syndrome – moderate)
5 - Dementia or chronic brain syndrome – severe or incompetent
9 - (Unknown)
Expanded Disability Status Scale

0.0 - Normal neurological exam
1.0 - No disability, minimal signs on exam
2.0 - Minimal disability
3.0 - Moderate disability, yet fully ambulatory
4.0 - Fully ambulatory without aid, up and about 12 hrs a day despite relatively severe disability. Able to walk without aid 500 meters.
4.5 - Fully ambulatory without aid, up and about much of the day, able to work a fully day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters.
5.0 - Ambulatory without aid for about 200 meters. Disability impairs full day activities
5.5 - Ambulatory for 100 meters, disability precludes full daily activities
6.0 - Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
6.5 - Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting.
7.0 - Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5 - Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day’s activities
8.0 - Essentially restricted to bed, chair or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms
8.5 - Essentially restricted to bed much of day, some effective use of arms, retains some self care functions
9.0 - Helpless bed patient, can communicate and eat
9.5 - Unable to communicate effectively or eat/swallow
10.0 - Death
Expanded Disability Status Scale

0 = Normal Neurological Exam
1 = Minimal Disability
2 = Increased Limitation in Walking Ability
3.5 = Require Assistance for Walking
5 = Restricted to a Wheelchair
7 = Bedridden

MS Disability Evolution - the “aHSCT Window”

Progression from EDSS 0-4 (inflammatory phase): between 1-32 years
Progression from EDSS 4-7 (degenerative phase): between 7-11 years
Below is a graph showing the average time a person spends in each EDSS level.
MRI BRAIN SCAN DONE

☐ Not done prior to HSCT

☐ Yes: Date of most recent MRI scan of brain: .......... - .......... - ..........  ☐ Date unknown

Results

Gadolinium-enhancing lesions present  ☐ Number.....................  ☐ None  ☐ Unknown
HSCT blocks inflammatory CNS activity
(Gd-contr. MRI lesions)

Patient 2
M/30 years.
RR-MS

Baseline
(1.5 months before HSCT)
17 Gd-contr. CNS lesions

EDSS 3.5

Post-HSCT
(6, 12, 24 and 36 months follow-up)
0 Gd-contr. lesions

EDSS 1.0

MS EBMT database
MS Subtype at baseline (n=374)

- Sec progr; 179
- Prim progr; 81
- Rel/Rem; 92
- Progr rel; 22

The European Group for Blood and Marrow Transplantation
HSCT for MS: Megafile analysis
Distribution for MS Type

The European Group for Blood and Marrow Transplantation

May 2011
MULTIPLE SCLEROSIS INDICATIONS

• RR phase, showing high inflammatory activity, both clinically and by MRI (Gd+ and/or new T2 lesions), who are rapidly deteriorating despite the use of one or more lines of approved treatments (level II).

• SP patients should be considered for HSCT only when some inflammatory activity is still evident (relapses or Gd+ lesions, and/or new T2 MRI lesions) and with a sustained and clinically relevant increase in disability in the previous year (level II).

• Patients who have lost the ability to walk (usually an EDSS upper limit of 6.5) must be excluded, except for ‘malignant’ forms (Marburg type) (level II).
DEFINITIONS IN MS EBMT committee

Pre-tt baseline = last assessment before mobilization or before conditioning regimen

Progression: defined clinically
- ↑ of existent neurologic disability or onset of new neurologic deficits compared to pre-tt baseline.
- ↑ at least 1 point of EDSS if pre-TP baseline EDSS ≤5 or ↑ of at least 0.5 point if baseline EDSS >5.
- ↑ disability <= from any MS-related or tt-related

Relapse: acute disease exacerbations or relapses characterized by worsening of existent neurologic disability or new neurologic deficits lasting >24hr not concomitant to infection/fever

A patient can experience a relapse and completely recover, with or without a specific treatment and will not be considered “progressed” if the EDSS is still < baseline.
CONDITIONING REGIMENS

• High intensity conditioning regimens (including irradiation at any dose), should be restricted to clinical trial setting (level III).

• Intermediate intensity conditioning regimens provide a balance between safety and efficacy, whilst facilitating data analysis and clinical trial planning (level II):
  • Cyclophosphamide 200mg/kg with polyclonal or monoclonal anti-T cell serotherapy is recommended generally;
  • For multiple sclerosis specifically BEAM + ATG (or other anti-T cell serotherapy) is recommended.
Lupus Erythematosus
Systemic Lupus Erythematosus

- *Systemic Lupus Erythematosus* (SLE) is a chronic autoimmune disease that can be fatal, the immune system attacks the body’s cells and tissue, resulting in inflammation and tissue damage.

- SLE can affect any part of the body, but most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system.

- The course of the disease is unpredictable, with periods of illness called *flares*, alternating with remissions.

- Can occur at any age, most common in young women (9/1).
ACR 1982 Classification Criteria:

4/11 criteria, either at present or in the past - strong chance for lupus

- Malar Rash
- Discoid Rash
- Photosensitivity
- Oral Ulcers
- Arthritis
- Serositis
- Renal Disorder
- Neurological Disorder
- Hematological Disorder
- Immunological Disorder
- Antinuclear Antibody

CENTRAL NERVOUS SYSTEM
Seizures, Paralysis, Neuropathies, Psychiatric Disorders, Headaches or migraines

EYE
Retinal exudates, Blindness, Conjunctivitis, Sjögrens Syndrome

SKIN COVERING
Baldness, Discoid LE, Butterfly Rash, Raynauds Syndrome, Photosensitivity, Mucosal Ulcers of Nose, Mouth and Vagina

KIDNEY
Renal Failure, Proteinuria, Oedema, Hypertension

GASTRO INTESTINAL TRACT
Poor Appetite, Vomiting, Diarrhoea

MUSCULOSKELETAL
Arthralgias, Arthritis and Myalgias

BLOOD
Decreased Platelets, Abnormal Autoantibodies

LINING MEMBRANES
Pericarditis, Pleurisy, Endocarditis

LYMPHADENOPATHY
Liver and Spleen Enlargement

REPRODUCTIVE
Menorrhagia, Amenorrhoea, Prematurity, Stillbirths

GENERALISED SYMPTOMS
Fatigue, Aching, Feverishness, Rashes, Weakness, Weight gain, or loss
SLE

- Anti-nuclear antibodies (ANAs, also known as anti-nuclear factor or ANF) are autoantibodies that bind to contents of the cell nucleus.

- In normal individuals, the immune system produces antibodies to foreign proteins (antigens) but not to human proteins (autoantigens). In some individuals, antibodies to human antigens are produced.

- There are many subtypes of ANAs (anti-Ro antibodies, anti-La antibodies, anti-Sm antibodies, anti-nRNP antibodies, anti-Scl-70 antibodies, anti-dsDNA antibodies, anti-histone antibodies, antibodies to nuclear pore complexes, anti-centromere antibodies and anti-sp100 antibodies).

- Present in about 5% of the general population

- Indicates that the immune system is altered

- Nearly 100% of people with lupus are ANA positive, not everyone with ANAs develops lupus
<table>
<thead>
<tr>
<th>Involvement/Clinical problem</th>
<th>Presence</th>
<th>Indication for HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>renal (biopsy type:_________)</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
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<tr>
<td>CNS (type:_________)</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
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<tr>
<td>PNS (type:_________)</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
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<tr>
<td>lung</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>serositis</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>arthritis</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>skin (type:_________)</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>haematological (type:_________)</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>vasculitis (type:_________)</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>other, specify:_____________</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
</tr>
</tbody>
</table>

Complement reduced □ No □ Yes □ Not evaluated

Antibodies studied □ No □ Yes □ Normal/Negative □ Elevated/Positive □ Not evaluated

Yes: ds DNA
Other, specify: ________________________________
unknown
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Recent onset (last 10 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.</td>
<td></td>
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</tr>
<tr>
<td>Psychosis</td>
<td>Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.</td>
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<td>8</td>
</tr>
<tr>
<td>Organic brain syndrome</td>
<td>Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.</td>
<td></td>
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<td></td>
<td>8</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.</td>
<td></td>
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<td>8</td>
</tr>
<tr>
<td>Cranial nerve disorder</td>
<td>New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.</td>
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<tr>
<td>Lupus headache</td>
<td>Severe, persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.</td>
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<tr>
<td>CVA</td>
<td>New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.</td>
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<td>8</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis.</td>
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<td>8</td>
</tr>
<tr>
<td>Arthritis</td>
<td>More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Myositis</td>
<td>Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Urinary casts</td>
<td>Hemato-granular or red blood cell casts.</td>
<td></td>
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<td></td>
<td>4</td>
</tr>
<tr>
<td>Hematuria</td>
<td>&gt;5 red blood cells/high power field. Exclude stone, infection or other cause.</td>
<td></td>
<td></td>
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<td>4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt;0.5 gm/24 hours. New onset or recent increase of &gt;0.5 gm/24 hours.</td>
<td></td>
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<td>4</td>
</tr>
<tr>
<td>Pyuria</td>
<td>&gt;5 white blood cells/high power field. Exclude infection.</td>
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<td>4</td>
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<tr>
<td>New rash</td>
<td>Ongoing inflammatory lupus rash.</td>
<td></td>
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<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.</td>
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<td>2</td>
</tr>
<tr>
<td>Mucosal ulcers</td>
<td>Ongoing oral or nasal ulcerations due to active lupus.</td>
<td></td>
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<td></td>
<td>2</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Classic and severe pericardial pain or rub or effusion or electrocardiogram confirmation.</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Low complement</td>
<td>Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.</td>
<td></td>
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<td>2</td>
</tr>
<tr>
<td>Increased DNA binding</td>
<td>&gt;25% binding by Farr assay or above normal range for testing laboratory.</td>
<td></td>
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<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>&gt;38°C. Exclude infectious cause.</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>&lt;100,000 platelets/mm 3 (x 10 9 /L).</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>&lt;3,000 white blood cells/mm 3 (x 10 9 /L). Exclude drug causes.</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**TOTAL SLEDAI SCORE =**
<table>
<thead>
<tr>
<th>Mild or Moderate Flare</th>
<th>Severe Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)</td>
<td>□ Change in SELENA-SLEDAI instrument score to greater than 12</td>
</tr>
<tr>
<td>□ New/worse:</td>
<td>□ New/worse:</td>
</tr>
<tr>
<td>- Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus</td>
<td>- CNS-SLE</td>
</tr>
<tr>
<td>- Nasopharyngeal ulcers</td>
<td>- Vasculitis</td>
</tr>
<tr>
<td>- Pleuritis</td>
<td>- Nephritis</td>
</tr>
<tr>
<td>- Pericarditis</td>
<td>- Myositis</td>
</tr>
<tr>
<td>- Arthritis</td>
<td>- Plt &lt;60,000</td>
</tr>
<tr>
<td>- Fever (SLE)</td>
<td>- Hemolytic anemia: Hb &lt;70 g/L or decrease in Hb &gt;30 g/L</td>
</tr>
<tr>
<td>□ Increase in prednisone, but not to &gt;0.5 mg/kg/day</td>
<td>□ Increase in prednisone to &gt;0.5 mg/kg/day, or hospitalization</td>
</tr>
<tr>
<td>□ Added NSAID or hydroxychloroquine for SLE activity</td>
<td>□ New cyclophosphamide, azathioprine, methotrexate for SLE activity</td>
</tr>
<tr>
<td>□ ≥1.0 increase in PGA score, but not to more than 2.5</td>
<td>□ Hospitalization for SLE activity</td>
</tr>
<tr>
<td></td>
<td>□ Increase in Physician’s Global Assessment score to ≥2.5</td>
</tr>
</tbody>
</table>
BILAG Index: 8 Systems

- General
- Mucocutaneous
- Neurologic
- Musculoskeletal

- Cardio-respiratory
- Vasculitis
- Renal
- Hematology

All features must be attributable to SLE, based on the scoring physicians “intention to treat,” and refer to last 4 weeks compared with prior disease activity.

0=Not present; 1=Improving; 2=Same; 3=Worse; 4=New or recurrence.
Or, Y/N or laboratory value where indicated.
SLE

- Corticosteroids
- Hydroxychlorquine (Plaquenil®)
- Aspirin
- Antimalarials
- Cytotoxics including cyclophosphamide, azathioprine, methotrexate
- Plasmapharesis/PE
- Thalidomide
- Anticoagulants
- Diaminodiphenylsulfone
- NSAIDs
- DHEA
Recommendations – SLE

• Whenever possible, HSCT in SLE should be performed in the context of a multicentre, clinical trial with well-defined endpoints, eligibility criteria, and in accordance with good clinical practice and appropriate regulatory requirements (level III).

• Current uncontrolled data suggest that HSCT can be considered as treatment for carefully selected subpopulations of patients with SLE early in their disease course, with reliably predicting poor-prognostic factors, according to combinations of demographic, clinical and laboratory markers (level II).
DEFINITIONS IN SLE  EBMT committee

- **Clinical success** = combined renal and extra renal remission, neither persistence nor ↑ disease activity in any organ system requiring a change in therapy (BILAG A scores) + independence from all IS other than MMF as maintenance and low dose CS < 10 mg daily. **Failure** = absence of clinical success.

- **Disease activity** = BILAG (from 0 to 72) and the SLEDAI (from 0 to 105) scores. **Disease damage** = SLICC/ACRR Damage Index (from 0 to 47) for SLE at baseline and rated quarterly during follow up.

- **Quality of Life** = SF 36 at baseline, quarterly throughout the follow up at 12 and 24 months.

- **Number of treatment failure** defined by the onset of either:
  1. **ESRD** requiring dialysis or transplantation.
  2. **Sustained doubling serum renal creat** confirmed by a 2nd serum creatinine values obtained at least four 4 weeks after the initial doubling (modeled on Brenner et al 2001).
  3. **Renal flare** defined as a) proteinuric with doubling the protu: creatinine ratio and a proteinuria > 1g/24 hours for pts < 0.5 g/24 hrs at inclusion or a protu ≥ 2 g/24 hrs for patients who were > 0.5 g/24 hrs at inclusion OR b) nephritic with a 25% increase in serum creatcreatinine value at inclusion + x 2 proteinuria reaching a minimum of 2 g/24 hrs plus hematuria (blood 2+ on dipstick) + cellular casts. Both a) and b) should be confirmed twice at 2 weeks interval.
  4. **Major extra renal flare**, defined as a BILAG score category A in one organ.
  5. **Requirements for IV steroids** steroids, plasmapheresis exchange, iv Immunoglobulins or any other immunosuppressive therapy to treat deterioration or exacerbation.

- **Number and timing of relapses** ↑ in disease activity in any organ system requiring a change in therapy (BILAG A scores) after prior clinical success at 2 years after AHSCT.

- **Presence of co-morbidities**

- **Immunological parameters**: C3, C4, anti DNA values, peripheral blood cells counts and blood lymphocytes immunophenotyping.
ADWP GUIDELINES - AIMS

- Support HSCT centres
  - with patient referrals by specialists
  - currently running a local trial

- Patient safety and benefit
  - Clinical teams and facilities
  - Patient selection (and exclusion), and clinical trials/studies
  - HSCT procedural aspects
  - ‘Quality’ of HSCT care i.e JACIE (or equivalent) accreditation
  - Follow up
  - Data reporting

- Future development of the field
Whenever possible, HSCT in AD should be performed in the context of a phase II or III clinical trial with well defined end points and eligibility criteria in accordance with good clinical practice and appropriate regulatory requirements.

Pre-HSCT evaluation of heart, lung, kidney and gastrointestinal function appropriate to the AD is critically important.

Patients with advanced cardiac disease (LVEF <50% in SSc, <40% in other indications, uncontrolled ventricular arrhythmias, pericardial effusions >1 cm), renal insufficiency (Cr Cl <40 mL/min per m² in SSc or <30 mL/min per m² in other indications), respiratory disease (DLCO <40% predicted, mean PAP <50mmHg in SSc, ventilatory impairment in MS) or active gastrointestinal bleeding should be excluded.
EBMT registry

• The high number of procedures reported to EBMT registry allows:

- a careful stratification for analysing outcomes on each AD diagnosis

- tight cooperation between transplant teams and the referring specialist is a key factor

- better selection and improved clinical management of the patients

- such a data may be important for further health care decision policy and would support the need for referring centres, with significant levels of activity and resources for adapted clinical care in treating rare ADs