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

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ABSTRACT

Background
Since autologous hematopoietic stem cell transplantation (HSCT) has been used since 1996 for treating severe autoimmune diseases (AD) refractory to approved treatments, we aimed to evaluate long term outcomes and to identify potential prognostic factors.

Design and Methods
This observational study (1996-2007) analysed all first AHSCT for AD reported to the European Group for Blood and Marrow Transplants (EBMT) registry. Primary end-points were overall survival (OS), progression-free survival (PFS) and the 100 days transplant related mortality (TRM).

Results
900 AD patients (64 % female, median 35 years) with first autologous HSCT were included, mainly: 345 multiple sclerosis, 175 systemic sclerosis, 85 lupus erythematosus, 89 rheumatoid arthritis, 65 juvenile arthritis, 37 hematological immune cytopenia. Overall, the 5 years OS was 85 % and PFS 43 %, varying widely according to AD type. By multivariate analysis, the day 100 TRM was associated with centre experience (p=0.003) and AD type (p=0.03). No significant influence of transplant technique could be identified. Age < 35 yrs (HR 1.37, 95%CI (1.1-1.7), p=0.004), autologous HSCT after 2000 (HR 1.47, 95%CI (1.16-1.86), p=0.0015) and diagnosis (p=0.0007) were associated with PFS.

Conclusions
This largest cohort studied worldwide shows that autologous HSCT can induce sustained remissions for more than 5 years in patients with severe AD refractory to conventional therapy. AD disease type, rather than transplant techniques, was the most relevant determinant of outcome. Results improved with time and were associated with centre experience. These data support ongoing and planned phase III trials to evaluate the place of autologous HSCT in the treatment strategy for severe AD.

Key words: autologous hematopoietic stem cell transplantation, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, total body irradiation, antithymocyte globulins, cyclophosphamide.

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Introduction

Autoimmune Diseases (ADs) are a family of more than 100 heterogeneous diseases, which affect 5 to 8 % of the population worldwide, and are characterised by aberrant activation of the immune system with failure of immune regulation to maintain adapted tolerance.[1] Although conventional immunosuppression and new biological agents can provide disease control in severely affected patients, such treatments are rarely curative and alternative strategies are needed.[2] In addition, severe forms of systemic ADs, such as multiple sclerosis (MS), systemic sclerosis (SSc), inflammatory arthritis as rheumatoid arthritis (RA), lupus erythematosus (SLE), or juvenile idiopathic arthritis (JIA) haematological immune cytopenia (HIC) and Crohn's disease are difficult to treat. Therefore, the personal and societal costs of the ADs and their treatments are high, accounting for short and long term significant morbidity and mortality. Following initial perspectives,[3] an international coordinated program was started under the auspices of the European Group for Blood and Marrow Transplants (EBMT) and the European League against Rheumatism (EULAR) to explore the role of intensive immunosuppression followed by Hematopoietic Stem Cell Transplantation (HSCT) in the treatment of severe ADs.[4] The concept arose from a large number of experimental data obtained both in genetically prone models of AD (lupus and diabetes) and in those obtained after immunisation towards a foreign antigen (Acute Experimental Arthritis and Acute experimental Encephalomyelitis) showing the possibility of *cure* with tolerance induction after allogeneic[5] and also after syngeneic (pseudo-autologous)[6] HSCT. The first consensus statement concerning the use of HSCT for treating severe ADs in 1995, stipulated the basic principles with regard to disease categories, patient selection, mobilisation, *in vitro* manipulation, conditioning and treatment.[3] Autologous was largely preferred to allogeneic hematopoietic transplantation due to lower risk of severe toxicity. Briefly, patients should be considered for HSCT if: a) diagnosed with an AD severe enough to have an increased risk of mortality or advanced and irreversible disability; b) the ADs has been unresponsive to conventional treatments; c) the HSCT can be undertaken before irreversible organ damage, so that significant clinical benefit can be achieved. The first case report of autologous hematopoietic stem cell transplantation for systemic sclerosis was published in 1996.[7]

Today, the EBMT registry includes a thousand HSCT performed for AD alone by January 2009, 350 others being reported in the US Bone Marrow Transplantation Registry (CIBMTR) and the rest in Asia. In 2003, Gratwohl et al reported the early survival, transplant-related mortality and disease response after autologous HSCT for AD among the first 473 patients registered in the EBMT data base.[8] Since then, increased use of the new biotherapies has modified the therapeutic panorama, but in the meanwhile focused publications on SSc,[9-12] MS (13) and SLE[14-16] have provided encouraging results from pilot series of institution trials using single disease response criteria. We therefore were interested to learn more about the longer term outcome of those originally reported with, in addition, newly recruited cases since then, and to analyse the determinants of the observed responses after a first autologous HSCT. Indeed, in our population with a longer follow-up, we found the influence of a centre effect on the Overall Survival.

Design and Methods

This is an observational study by the Autoimmune Disease Working Party of the EBMT. Data were collected by questionnaire or by the electronic EBMT data management system ProMISe (*www.ebmt.org*) and updated annually. The study was approved by the review boards of each participating institutions and by the EBMT board committee. Informed consent was obtained from all patients before HSCT. Thanks to a specific questionnaire sent to each center in 2007, 67% of patients alive were updated in 2007. All EBMT participating centres were requested to report all consecutive transplants. An accreditation program has been developed to harmonize the standard of care and validate data reporting through all EBMT centres (*www.jacie.org*). The methodology used for data collection according to each disease category and the activity index used for determing that patients had progressed were the same as in Gratwohl report.[8] All consecutive AD patients reported to the EBMT registry data base from 1996 to December 2007 were included in this study, which was conducted according to the STOBE principles.[15]

HSCT procedure

Standard techniques, as used in autologous HSCT for hematological malignancies were employed using either bone marrow (BM), peripheral blood stem cells (PBSC) or both stem cell products for stem cell sources. Peripheral blood stem cells were used as the stem cell source for the majority of the patients (93%). Mobilisation and collection of peripheral blood stem cells (PBSC) was achieved mostly with Cyclophosphamide (1.5 - 4 g/m^2) in combination with granulocyte-colony stimulating factor (G-CSF), or with G-CSF alone according to local protocol. In vitro purging before AHSCT (44%) was performed according to local protocol, using either CD34$^+$ positive selection (92%) or by negative purging of lymphocytes subsets by monoclonal antibodies, particularly anti-CD52 (CAMPATH 1), anti-CD3, anti-CD19, or anti-CD20 (8%). The conditioning regimen used either Total Body Irradiation (TBI) (7%) or chemotherapy alone (93%), including various reported combinations based on Cyclophosphamide (at 150 or 200 mg/kg total dose) (52%), Busulfan (4%), BEAM (Carmustine, Cytarabine, Melphalan, and Etoposide) (34%). ATG was used in 55% of patients. To analyse the effect of the various conditioning regimen on the outcomes, these were subgrouped as previously published into a) high intensity regimen, including any Busulfan or TBI containing regimen, b) low intensity restricted to Cyclophosphamide alone, Melphalan alone and Fludarabine-based regi-

mens, or c) intermediate regimen, including all the other combinations. Experience of the centre was based on the number of autologous HSCT for AD carried out per centre during the studied period.

Statistical analysis

Progression free survival (PFS) was defined as survival without evidence of relapse or progression. Progression was considered as any increase of disease activity index[8] as compared to baseline. Overall survival (OS) was defined as time to death, irrespective of the cause. The 100 days Transplant Related mortality (TRM) was defined as death without AD relapse or progression. Cumulative incidence curves were used for 100 days TRM[16,17] and compared using the Gray's test as a competing event.[16] Probabilities of PFS were calculated using the Kaplan-Meier estimate; the log-rank test was used for univariate comparisons. For all prognostic analyses, continuous variables were categorised and the median was used as a cut-off point. Associations of patient, disease and graft characteristics with outcomes were evaluated in multivariate analyses, using Cox proportional hazards for PFS. Factors associated with a p value less than 0.15 by univariate analysis and factors with clinical relevance were included in the final model. All tests were two-sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analysis was performed with SPSS 15.0 (Inc., Chicago, USA) and SPlus 6.1 (MathSoft, Inc, Seattle) software packages.

Results

Transplant population

This study report concentrates on 900 patients, 64% female, with a median age of 35 years (range: 2.7-76) who underwent a first autologous HSCT for treating a severe autoimmune disease (AD) in 172 institutions from 27 countries. Rheumatological (60%) and neurological (33%) ADs accounted for the major disease categories, whereas haematological autoimmune cytopenia and most recently reported, inflammatory bowel disease, were a small minority. Six AD categories represented the major indications, namely: Multiple Sclerosis (MS=345 patients), Systemic Sclerosis (SSc=175 patients), Rheumatoid Arthritis (RA=89 patients), Systemic Lupus Erythematosus (SLE=85 patients), Juvenile Idiopathic Arthritis (JIA=65 patients), Haematological Immune Cytopenia (HIC=37) and other indications (Other=104). Nine patients received a second autologous HSCT.

Transplant activity

Significant changes in the indications appeared over time. For RA as indication, autologous HSCT has virtually disappeared since 2001 due to the availability of new biologic agents. It accounted for a drop in the overall transplant activity, which nonetheless remained above 50 autologous HSCT for AD per year (Table 1). Differences in patients' characteristics and in treatment variables according to their original AD were also noticeable (Table 2). Within the major ADs categories, SSc and RA patients were older than the median of 35 years. As expected, a high percentage of female was seen in RA (73%), SSc (71%) and SLE (86%) patients compared to the others, the highest proportion of females being classically observed among SLE patients. Disease duration before autologous HSCT varied widely between the major ADs categories and the median interval time between diagnosis and transplant was shorter for SSc (30 mo) and much longer for RA (86 mo) and MS (77 Mo) patients.

Table 1. Overall and yearly activity of autologous Haematopoietic Stem Cell Transplantation (HSCT) for all cases of severe Autoimmune Diseases (ADs) (n =900) reported to the European Group for Blood and Marrow Transplantation (EBMT) data registry from 1996 to December 2007.

Year of autologous HSCT	MS	SSc	RA	SLE	JIA	HIC	Others	Total
1996	18	7	1	1	0	2	1	30
1997	6	4	12	3	6	3	4	38
1998	28	14	8	12	11	7	9	89
1999	36	12	47	11	12	7	14	139
2000	22	20	11	17	10	3	5	88
2001	33	13	3	13	8	3	6	79
2002	33	14	2	5	5	2	9	70
2003	19	13	0	5	7	1	7	52
2004	33	18	0	6	1	4	13	75
2005	35	17	3	6	3	1	15	80
2006	52	22	1	4	2	3	15	99
2007	30	21	1	2	0	1	6	61
Total	345	175	89	85	65	37	104	900

Multiple sclerosis (MS, n=345), Systemic sclerosis (SSc, n=175), rheumatoid arthritis (RA, n=89), Systemic lupus erythematosus (SLE, n=85), juvenile Idiopathic arthritis (JIA, n=65), hematological immune cytopenia (HIC, n=37) and others (all other ADs, n= 104) .

Outcomes

On the overall population, the 5 years Overall Survival (OS) was 85% (95% CI: 79%-83%) (Figure 1A), the Progression Free Survival (PFS) was 43% (95% CI: 39%-47%) (Figure 1B) and the 100 d TRM was 5% ((95% CI: 3%-7%). The causes of death are summarised in table 3. At the time of analysis (December 2007), 789 patients were alive and 111 had died: 43 (38.7%) from their original disease and 59 (53.1%) of transplant related causes (Table 3). Infections (45.7%) were the first cause of TRM. Death due to cardiac toxicity (8.4%) was not related to a specific type of conditioning. The 100d TRM was 2% (95% CI: 0%-4%) for MS, 6% (95% CI: 2%-10%) for SSc, 1% (95% CI: 0%-3%) for RA, 11% (95% CI: 5%-17%) for SLE, 11% (95% CI: 6%-22%) for JIA and 8% (95% CI: 0%-18%) for HIC depending on AD type ($p<0.001$). Five years after HSCT: a) the PFS was 45% (95% CI: 38%-52%) for MS, 55% (95% CI: 46%-64%) for SSc, 18% (95% CI: 9%-27%) for RA, 44 % (95% CI: 32%-56%) for

Table 2. Patients (n=900) with severe Autoimmune Disease (AD) and graft characteristics at time of first autologous Hematopoietic Stem Cell Transplantation (HSCT) as reported to the EBMT registry from 1996 to December 2007.

	MS	SSc	RA	SLE	JIA	HIC	Others	Total
N autologous HSCT	345	175	89	85	65	37	104	900
N (%) female	210 (61%)	123(71%)	65(73%)	73 (86%)	32 (49%)	19 (51%)	56 (54%)	578 (64%)
Age at Tx (yrs)	35 (14-65)	41 (8-69)	42 (22-64)	28 (9-56)	11 (4.2-49)	35 (4-76)	41 (2.7-72)	35 (2.7-76)
Disease duration (mo)	77 (0.5-351)	30 (2.6-256)	86 (21-284)	58 (2-396)	74 (11-233)	42 (3-378)	49 (0.8-494)	62 (0.5-494)
Follow-up (mo)	31 (0.5-121)	34 (0.5-110)	28 (0.5-110)	25 (2-123)	67 (2.5-111)	56 (1-132)	24 (0.5-113)	34 (0.5-148
Source of HSC								
BM	16	4	1	11	29	2	2	65
PBSC +/- BM	326 (95%)	168 (98%)	88 (99%)	74 (87%)	36 (55%)	35 (95%)	100 (98%)	827 (93%)
Missing	3	3	0	0	0	0	2	
Purge								
No	215	81	46	45	11	15	60	473
Yes	115 (35%)	80 (50%)	42 (48%)	35 (44%)	51 (82%)	20 (57%)	33 (35%)	376 (44%)
Missing	15	14	1	5	3	2	11	51
If yes, method								
CD34	92	48	31	19	21	16	15	242
Other CD	0	1	2	1	5	1	0	10
Campath	3	6	0	1	1	0	0	11
Not specified	20	25	9	14	24	3	18	113
Missing	0	1	0	0	0	0	0	1
Conditioning								
TBI	16	4	1	13	24	2	2	62
Cyclo alone	8	60	47	6	3	4	11	139
Cyclo + other	25	49	7	18	15	11	16	141
Melphalan alone	2	2	0	3	0	5	13	25
Fludarabin based	4	4	1	3	7	3	5	27
Busulfan based	15	0	3	2	1	1	2	24
BEAM	168	2	1	4	0	2	4	181
Other chemo	101	48	29	33	13	8	41	273
Missing	6	6	0	3	2	1	10	28
Low	14	66	48	12	10	12	29	191
Intermediate	193	51	8	22	15	13	20	322
High	31	4	4	15	25	3	4	86
Missing	107	54	29	36	15	9	51	301

Multiple Sclerosis (MS); Systemic Sclerosis (SSc); Rheumatoid arthritis (RA); Systemic Lupus Erythematosus (SLE); Juvenile Idiopathic Arthritis (JIA); Haematological Immune Cytopenia (HIC) and others (all other Autoimmune Diseases); N = number; Tx = autologous Hematopoietic Stem Cell Transplantation; EBMT: European Group for Blood and Marrow Transplantation; BM: bone marrow; HSC: hematopoietic Stem Cells; PBSC: peripheral blood stem cells; TBI: total body irradiation; Cyclo: cyclophosphamide; BEAM = carmustine, cytarabine, melphalan and etoposide; mo = month.

SLE, 52% (95% CI: 38%-66%) for JIA and 34 % (95% CI: 16%-52%) for HIC; b) the OS was 92% (95% CI: 88%-96%) for MS, 76% (95% CI: 69%-83%) for SSc, 94% (95% CI: 87%-100%) for RA , 76% (95% CI: 66%-86%) for SLE, 82% (95% CI: 72%-92%) for JIA and 80% (95% CI: 66%-94%) for HIC depending primarily on AD type (p<0.0001).

Factors associated with outcome

Table 4 summarizes the results of the univariate (Table 4A) and multivariate (Table 4B) analysis of prognostic factors on 100d TRM, PFS and OS. By multivariate analysis (Table 4B), the day 100 TRM varied according to the original diagnosis (p=0.003) and was lower in experienced centres (HR 0.32, 95% CI (0.16-0.69), p=0.003). In addition to the influence of original diagnosis (p=0.0007), the age <35 yrs (HR 1.37, 95% CI (1.1-1.7), p=0.004) and an autologous HSCT performed after December 2000 (HR 1.47, 95% CI (1.16-1.86, p=0.0015) were associated with a higher PFS.

The original diagnosis (p=0.0005) was a strong determinant of the OS, and the centre experience (HR 2.49,

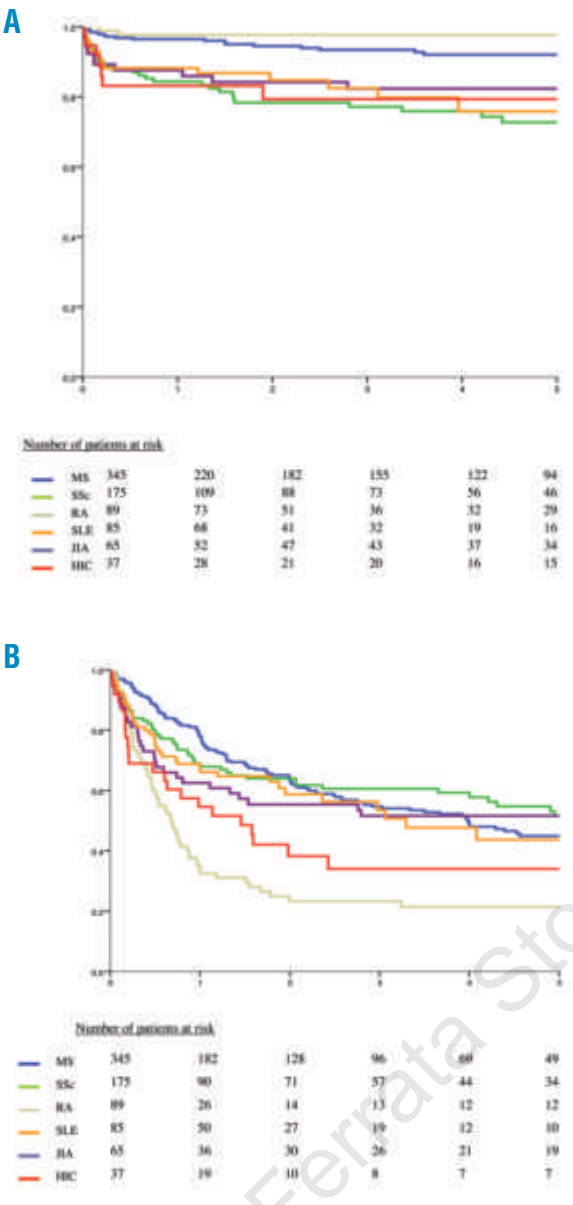

Figure 1 A. Overall survival of patients with autologous Hematopoietic Stem Cell Transplantation for severe Autoimmune Diseases (AD) depending on the disease type in the 6 major AD categories (Multiple Sclerosis in blue (MS); Systemic Sclerosis in green (SSc); Rheumatoid arthritis in grey (RA), Systemic Lupus Erythematosus in orange (SLE); Juvenile Idiopathic Arthritis in purple (JIA); Haematological Autoimmune Cytopenia in red (HIC) as reported to the EBMT data base from 1996 to 2007 (n=900 patients) Kaplan Meier curves for the observed a) Overall Survival and b) Progression Free Survival. **B.** Progression-Free Survival.

95% CI (1.62-3.82), $p<0.0001$), the use of Peripheral Blood Stem Cells (HR 2.52, 95% CI (1.33-4.79), $p<0.005$), the age < 35 yrs (HR 1.72, 95% CI (1.13-2.62), $p=0.01$) and a disease duration>median before HSCT (HR 1.45, 95% CI (0.98-2.14), $p=0.06$) were associated with a higher OS (Table 4B).

Table 3. Causes of death after autologous HSCT for severe ADs in 900 treated patients as reported to the EBMT data base from 1996 to December 2007.

Cause of death	MS n=345	SSc n=175	RA n=89	SLE n=85	JIA n=65	HIC n=37	Others n=104	Total n=900
Original disease	8	23	0	5	2	1	4	43
Transplant related	13	12	2	11	7	6	8	59
Cardiac toxicity	1	1	0	2	0	0	1	5
Hemorrhage	2	2	0	0	0	1	0	5
Failure/ rejection	0	0	0	0	0	1	0	1
Infection	5	4	2	7	4	2	3	27
Interstitial pneumonitis	2	1	0	0	0	2	0	5
Graft-versus-host disease*	0	0	0	0	0	0	1	1
Second malignancy**	1	2	0	1	0	0	1	5
Others	2	2	0	1	3	0	2	10
Unknown	1	1	1	2	2	0	2	9

*HSCT: hematopoietic Stem Cell Transplantation; EBMT: European Group for Blood and Marrow Transplantation; Multiple Sclerosis (MS); Systemic Sclerosis (SSc); Rheumatoid arthritis (RA); Systemic Lupus Erythematosus (SLE); Juvenile Idiopathic Arthritis (JIA); Haematological Immune Cytopenia (HIC) and others (all other Autoimmune Diseases); n: number; PBSC: peripheral Blood Stem Cells. After failure from autologous HSCT, patient had been treated by allogeneic HSCT and eventually died from GvHD. ** The 5 secondary malignancies were: acute myeloid leukemia (MS), bronchus carcinoma (SSc), oesophagus carcinoma (SSc), refractory anemia with excess of blats (SLE) and post transplant lymphoproliferative disease (others: mixed connective tissue disease).*

Discussion

The aim of this paper was to merge the longer term follow-up of the 473 patients previously reported by the EBMT in 2003[8] with the cases reported to the Registry thereafter, in order to analyse the determinants of the clinical responses in 900 severe ADs patients treated by a first autologous HSCT, which is the largest number analysed worldwide so far. Our data confirm that autologous HSCT is a valid therapeutic option for patients with an AD progressing despite standard therapy.[2,3,20]

To make this analysis feasible, the data were obtained from the EBMT registry using a large international network after ten years of an EBMT-EULAR collaboration, including 549 member centres. Free and voluntary data reporting, in accordance with the EBMT rules (*www.ebmt.org*), was highly encouraged in the initial consensus.[3] Teams used different transplant techniques, but most of EBMT participating centres did adhere to the broad indications and the optimum treatment methods published early in the program,[3,4] which basic principles are still valid. All centres were subjected to random audits, as part of an audit by EBMT for all of the transplant centers, to control the consistency of report-

Table 4. Univariate (A) and multivariate (B) analysis of prognostic factors in 900 AD patients treated by autologous HSCT and reported to the EBMT data base from 1996 to December 2007. In multivariate analysis only statistically significant variables were reported.

	100d TRM	3 yrs PFS	3 yrs OS
A.			
AD categories			
MS	2 (0-14)	55 (49-61)	93 (89-97)
SSc	6 (2-10)	63 (55-71)	80 (66-94)
RA	1 (0-3)	23 (13-33)	98 (94-100)
SLE	11 (55-17)	54 (42-46)	87 (79-95)
JIA	11 (6-22)	52 (38-66)	82 (72-92)
HIC	8 (0-18)	34 (16-52)	80 (74-86)
Others	6 (4-6)	46 (34-58)	83 (75-91)
	< 0.0001	< 0.0001	< 0.0001
AD patient's age			
Age <35 yrs	6 (4-8)	56 (50-62)	89 (85-93)
Age >35 yrs	4 (2-6)	46 (40-52)	87 (83-91)
	0.45	0.001	0.13
Sex			
Male	4 (2-6)	53 (47-59)	88 (84-92)
Female	5 (3-7)	50 (44-56)	87 (81-93)
	0.45	0.35	0.32
Year of autologous HSCT			
year <2001	5 (3-7)	43 (37-49)	86 (82-90)
year >2001	4 (2-6)	59 (53-65)	89 (85-93)
	0.53	<0.0001	0.27
Interval between diagnosis and autologous HSCT			
<median	6 (4-8)	55 (49-61)	84 (81-88)
>median	3 (1-5)	48 (42-54)	90 (86-94)
	0.04	0.58	0.007
Source of stem cells			
Bone Marrow	9 (3-15)	47 (33-61)	80 (70-90)
PBSC	4 (2-6)	51 (47-55)	88 (86-90)
	0.08	0.63	0.07
Conditioning regimen			
Low intensity	4 (2-6)	46 (38-54)	87 (81-93)
Intermediate intensity	3 (1-5)	57 (51-63)	90 (86-94)
High intensity	5 (1-9)	46 (34-58)	83 (75-91)
Not specified	6 (4-8)	49 (41-57)	87 (81-93)
	0.51	0.011	0.23
TBI			
no TBI	5 (3-7)	50 (46-54)	88 (86-90)
TBI	3 (0-7)	55 (41-69)	86 (76-96)
	0.58	0.26	0.52
Purging			
no purge	5 (3-7)	51 (45-57)	90 (78-100)
Purge	4 (2-6)	50 (44-56)	86 (82-90)
	0.28	0.37	0.15
Center experience			
Nb patients < 13 (n=441)	7 (5-9)	48 (42-54)	83 (79-87)
Nb patients >13 (n=421)	3 (1-5)	53 (47-59)	92 (90-94)
	0.004	0.45	0.0001

ed data. All registry data analyses are subjected to limitations.[17] One drawback was the missing values concerning the details of conditioning chemotherapy protocols, when TBI was not used. However, the high number of procedures reported to EBMT registry allowed a careful stratification for analysing outcomes on each AD diagnosis.[17,18] Autologous HSCT was performed in several major indications since 1996, namely: MS,[13,21,22]

Table 4. **Univariate (A) and multivariate (B) analysis of prognostic factors in 900 AD patients treated by autologous HSCT and reported to the EBMT data base from 1996 to December 2007. In multivariate analysis only statistically significant variables were reported.**

100 d TRM*	p	HR	95.0% IC
B			
Center experience	0.003	0.32	0.16-0.69
Diagnosis	0.03		
MS		1.78	0.21-14.8
SSC		4.45	0.56-35.4
RA			
SLE		9.8	1.25-76.8
JIA		7	0.81-60.8
HIC		5.23	0.54-50.6
other		4.01	0.48-33.4
PFS**			
Age < 35yrs	0.004	1.37	1.1-1.7
Year ≥ 2001	0.0015	1.47	1.16-1.86
Diagnosis	0.0007		
MS		0.86	0.69-1.07
SSC		0.68	0.53-0.87
RA		1	
SLE		0.96	0.72-1.3
JIA		0.94	0.66-1.34
HIC		1.22	0.84-1.77
other		0.97	0.73-1.29
OS			
Age <35 yrs	0.01	1.72	1.13-2.62
Diagnosis	0.0005		
MS		0.65	0.42-1
SSC		1.77	1.19-2.6
RA		1	
SLE		2.06	1.29-3.27
JIA		1.17	0.61-2.21
HIC		1.18	0.6-2.32
Other		1.01	0.59-1.69
Interval between diagnosis and autologous HSCT > median	0.06	1.45	0.98-2.14
PBSC *vs.* bone marrow	0.005	2.52	1.33-4.79
Centers experience	<0.0001	2.49	1.62-3.82

**Adjusted for interval from diagnosis to transplant and source of stem cells; **adjusted on conditioning.*

SSc,[9,12] RA,[20,25] SLE,[13-16] JIA,[23,24] and HIC[26] and as the experience grew, other ADs were transplanted.[27,28] Evaluation of efficacy is not always obvious and varies according to the type of AD. In MS, which was the most frequently transplanted AD, disability progression can be related to the neuro-degeneration, which is part of the most advanced (Secondary Progressive) phase of the disease.[21,22] For rheumatological and haematological diseases, progression is usually associated with the relapse of the inflammatory activity. However, the Progression Free Survival at 5 years of 43 % may be the most accurate estimate for the overall outcome after autologous HSCT for severe AD patients, refractory to standard therapy.

The PFS varied according to the type of AD. In the majority of RA patients, the effect of the autologous HSCT was rather limited. Indeed, the introduction of new targeted biological treatments has modified the therapeutic panorama in the past few years with a drop of activity for Inflammatory Arthritis due to wider use and efficacy of the anti TNF agents,[20] whilst standard treatment of SSc has not significantly improved in the last ten years for poor prognosis patient.[29] All these factors contributed to change diagnosis distribution in patients undergoing autologous HSCT after the year 2000. SSc and HIC patients were referred to autologous HSCT rather earlier than RA, MS and SLE patients, illustrating the heterogeneity of each AD category before being considered refractory to standard therapy. Although the effect of age on the outcome could also be related in part to the type of AD, multivariate analysis revealed that the PFS improved in patients under 35 years of age. Indeed, differences in the spontaneous evolution of each AD type may also influence the long term outcome after autologous HSCT.

The Overall Survival at 5 years was 85%. It appeared higher in RA and MS than in SLE and SSc. In severe RA and MS patients selected for autologous HSCT, spontaneous disease progression evolves towards extensive disability at 10 years, with a life expectancy 5 to 10 years shorter than normal controls.[30] On the other hand, intrinsic immunodepression in SLE[1] and major vital organ involvement present in severe SLE or SSc patients eligible for autologous HSCT significantly impair their spontaneous survival, which was estimated between 30 and 50 % at 5 years for SSc[31] and 75 to and 80% at ten year for SLE.[32] On the overall EBMT registry data population, the Transplant Related Mortality (5 %) has clearly improved since the earlier reports on a smaller number of patients in 2001 (12%).[8] There were more deaths from the original disease than from the transplant procedure in SSc patients as opposite to other diagnoses, reflecting a different disease-related clinical evolution. Fatal infections appeared more frequent in SLE patients compared to other groups (39% *vs.* 22%, p=0.12), but the difference did not reach statistical significance. Multivariate analysis revealed a centre effect for autologous HSCT in ADs, influencing the 100d TRM and the OS. The centres gained experience with increased activity, as previously shown in autologous HSCT for hematological malignancies.[33] This centre effect, presumably due to better patient selection and clinical monitoring during and after the procedures, may contribute to heterogeneous perceptions about the risk and benefit ratio of autologous HSCT in ADs. Within this context, a tight cooperation between transplant teams and the referring specialist is key factor. Such results may be of note 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.[34] Intensity of the conditioning regimen, need for a myeloablative schedule and for graft manip-

ulation have been extensively discussed in the context of HSCT for ADs. In the present study, no significant correlation between the intensity of conditioning regimen and TRM was found, possibly due to the extremely low number of considered events with decreased TRM in the recent years. By univariate analysis, the intensity of conditioning regimen influenced the 3 years PFS, but this was not confirmed on multivariate analysis. Graft manipulation was employed in 44% of the reported procedures, largely based on laboratory studies and hypothetical risk of re-infusion of pathogenic T-cells within the graft. However, this procedure is associated with more severe immunosuppression and might result in higher toxicity. So far, no data have yet provided support for graft manipulation strategies as a mean of improving outcome.[2,8,20,3] In the present study, no significant association was found between graft purging and TRM nor PFS. However, this finding is limited by the heterogeneity of both groups (manipulated and unmanipulated grafts) with regard to the conditioning regimen that may have been applied. The value of graft manipulation in the setting of ADs is therefore still elusive and merits further investigation. Peripheral blood as the stem cells source appeared to improve OS in multivariate analysis. The main reason for using bone marrow as the source of cells for HSCT in ADs is to reduce the number of T-cells in the graft. However, evidence that graft T-cell content contamination may impact on the relapse rate is still lacking, and therefore the higher safety of using PBSC is to be preferred. A few studies reported safety and short term efficacy of high dose cyclophosphamide alone for treating lupus and multiple sclerosis.[36] They were based on the concern of infusing autoreactive cells within the graft. However, it has now become evident, in the setting of HSCT, that high dose cyclophosphamide for the mobilisation followed by the conditioning regimen and stem cells infusion both aim at resetting the autoimmune response and inducing long term tolerance via fundamental changes of the immune system.[37,38] Indeed, several translational studies have shown that clinical improvements after HSCT in systemic sclerosis,[39] multiple sclerosis,[40] juvenile arthritis[41] and systemic lupus erythematosus[42] patients can be associated with drastic reactivation of thymic activity, including the restoration of a new polyclonal T cell repertoire[39–41] and *de novo* induction of thymus derived natural Treg cells[40–41] which are essential for restoration of peripheral tolerance for autoantigens, or with the elimination of autoantibody producing cells.[42]

The improved PFS since 2000 on multivariate analysis demonstrated a learning effect over the years. As the program proceeded, certain clinical parameters and treatment related factors emerged as being associated with an unacceptable risk, such as a mean pulmonary artery pressure >50 mm Hg in SSc,[9,10,12,43] high disability scores in MS[21,22] and total body irradiation (TBI) without lung shielding in SSc.[11] Broad diffusion of these findings via international collaborative efficient networks with free and open partnership, and publication of consensus reports[4,43] were important to develop autologous HSCT in ADs. Improved PFS over the years could also be linked to the increased experience per centre and to the drop out in autologous HSCT activity for RA. In conclusion, this follow-up of the report by Gratwhold *et al*.[8] further confirms the value of autologous HSCT in patients with severe AD. The original diagnosis appears as the most relevant prognostic factor, reflecting the high clinical and biological heterogeneity of these diseases. Importantly, the present study, obtained on a higher number of patients with longer term follow-up, led to a novel conclusion: the centre experience was also an independent variable in determining the transplant related mortality and the overall survival. Better selection and improved clinical management of the patients, effective collaboration between the referring specialists and the haematological teams, may account for these findings. All these determinants contributed to improve the overall PFS since 2000, illustrating a learning curve effect with time. These results sum up ten years of an EBMT-EULAR international collaborative network and form the basis for future directions in the field. They strongly support the ongoing European and North American phase III trials in severe ADs, aimed to compare autologous HSCT with standard therapies in SSc (namely, the ASTIS trial (*www.astistrial.com*) in Europe and the SCOT trial (*www.sclerodermatrial.org*) in North-America), MS (*ASTIMS, www.astims.org*), Crohn's disease (*ASTIC, astic@nottingham.ac.uk*) and SLE (ASTIL).

Appendx

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Authorship and Disclosures

DF participated in the concept of the study, methodology, data acquisition, data interpretation and manuscript writing; ML participated in the statistical and

results sections (statistical analysis of the data); AT participated in the concept, data gathering and writing sections of this article; AF, GLM and J participated in the multiple sclerosis analysis; JVL participated to the preparation of this article; TK participated in the sections methods and findings. JM participated to the study design and coordination and contributed to writing the manuscript; IK participated in the treatment of patients, data acquisition and final corrections; VC participated in the data management; AM participated in the introduction and discussion section; AG participated in the design, analysis and writing and RS participated in the study by reviewing the whole paper and in his position as the EBMT Autoimmune Diseases Working Party Chairman.

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