

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

<sup>1</sup>Internal Medicine, Saint Louis Hospital, Paris, France; <sup>2</sup>Hôpital Saint Antoine, Service d'hématologie et Thérapie Cellulaire, AP-HP, UPMC Univ Paris 06, UMR-S 938, CEREST-TC EBMT, Paris, France; <sup>3</sup>Rheumatology, Rheumatologische Universitätsklinik, Basel, Switzerland; <sup>4</sup>Neurology and Haematology, The George Papanicolaou Hospital, Thessaloniki, Greece; <sup>5</sup>Neurosciences, Ophthalmology and Genetics, Univ. of Genova, Genova, Italy; <sup>6</sup>Institute of Cellular Medicine, Newcastle Univ., Newcastle Upon Tyne, United Kingdom; <sup>7</sup>Hematology, Hospital of Nanjing, Nanjing, China; <sup>8</sup>Clinical Haematology, Charles Univ. Prague, Prague, Czech Republic; <sup>9</sup>Hematology Dept., St Vincents Hospital, Sydney, Australia; <sup>10</sup>Immunology, Rheumatology and Autoimmune Diseases, Univ. of Tübingen, Tübingen, Germany; <sup>11</sup>INSERM UMR-S 938, UPMC Univ Paris 06, Paris, France; <sup>12</sup>Haematology, Ospedale di San Martino, Genova, Italy; <sup>13</sup>Haematology, Kantonspital Basel, Basel, Switzerland, and <sup>14</sup>BMT Unit, UO Ematologia, Policlinico Careggi, Florence, Italy

## ABSTRACT

### Background

Autologous hematopoietic stem cell transplantation has been used since 1996 for the treatment of severe autoimmune diseases refractory to approved therapies. We evaluated the long-term outcomes of these transplants and aimed to identify potential prognostic factors.

### Design and Methods

In this observational study we analyzed all first autologous hematopoietic stem cell transplants for autoimmune diseases reported to the European Group for Blood and Marrow Transplantation (EBMT) registry between 1996-2007. The primary end-points for analysis were overall survival, progression-free survival and transplant-related mortality at 100 days.

### Results

Nine hundred patients with autoimmune diseases (64% female; median age, 35 years) who underwent a first autologous hematopoietic stem cell transplant were included. The main diseases were multiple sclerosis (n=345), systemic sclerosis (n=175), systemic lupus erythematosus (n=85), rheumatoid arthritis (n=89), juvenile arthritis (n=65), and hematologic immune cytopenia (n=37). Among all patients, the 5-year survival was 85% and the progression-free survival 43%, although the rates varied widely according to the type of autoimmune disease. By multivariate analysis, the 100-day transplant-related mortality was associated with the transplant centers' experience ( $P=0.003$ ) and type of autoimmune disease ( $P=0.03$ ). No significant influence of transplant technique was identified. Age less than 35 years ( $P=0.004$ ), transplantation after 2000 ( $P=0.0015$ ) and diagnosis ( $P=0.0007$ ) were associated with progression-free survival.

### Conclusions

This largest cohort studied worldwide shows that autologous hematopoietic stem cell transplantation can induce sustained remissions for more than 5 years in patients with severe autoimmune diseases refractory to conventional therapy. The type of autoimmune disease, rather than transplant technique, was the most relevant determinant of outcome. Results improved with time and were associated with the transplant centers' experience. These data support ongoing and planned phase III trials to evaluate the place of autologous hematopoietic stem cell transplantation in the treatment strategy for severe autoimmune diseases.

Key words: autologous hematopoietic stem cell transplantation, autoimmune diseases, multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, hematologic immune cytopenia, total body irradiation, antithymocyte globulins, cyclophosphamide.

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Correspondence: Dominique Farge, Service de Médecine Interne et Unité INSERM U 976, Hôpital Saint-Louis, Assistance-Publique Hôpitaux de Paris, Paris-7 Université Denis Diderot, 1 avenue Claude Vellefaux, 75 010 Paris France. E-mail: dominique.farge-bancel@sls.ap-hop-paris.fr

## Introduction

Autoimmune diseases are a family of more than 100 heterogeneous conditions that affect 5 to 8% of the world's population, and are characterized by aberrant activation of the immune system with failure of immune regulation to maintain adapted tolerance.<sup>1</sup> 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.<sup>2</sup> Indeed, severe forms of systemic autoimmune diseases, such as multiple sclerosis (MS), systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), hematologic immune cytopenia (HIC) and Crohn's disease are difficult to treat. The personal and societal costs of autoimmune diseases and their treatments are high, including significant short- and long-term morbidity and mortality. Following initial perspectives,<sup>3</sup> an international coordinated program was started under the auspices of the European Group for Blood and Marrow Transplantation (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 autoimmune diseases.<sup>4</sup> The concept of transplantation therapy arose from a large body of experimental data, obtained both in genetically prone models of autoimmune disease (lupus and diabetes) and after immunization against foreign antigens (acute experimental arthritis and encephalomyelitis), showing the possibility of a 'cure' with tolerance induction after allogeneic<sup>5</sup> or syngeneic (pseudo-autologous)<sup>6</sup> HSCT. The first consensus statement concerning the use of HSCT for treating severe autoimmune diseases in 1995 set out the basic principles with regard to disease categories, selection of patients, stem cell mobilization, *in vitro* manipulation, conditioning and treatment.<sup>3</sup> Autologous HSCT was largely preferred to allogeneic transplantation because of the lower risk of severe toxicity. Briefly, patients with autoimmune diseases can be considered for HSCT if: (i) their disease is severe enough to cause an increased risk of mortality or advanced and irreversible disability; (ii) the disease has been unresponsive to conventional treatments; and (iii) the HSCT can be undertaken before irreversible organ damage, so that significant clinical benefit can be achieved. The first case report of autologous HSCT for SSc was published in 1996.<sup>7</sup>

As of January 2009, the EBMT registry includes data on 1,000 HSCT performed for autoimmune diseases alone, 350 transplants have been reported to the US Bone Marrow Transplantation Registry (CIBMTR) and others have been performed in Asia. In 2003, Gratwohl *et al.* reported the early survival, transplant-related mortality and disease response after autologous HSCT for autoimmune diseases among the first 473 patients in the EBMT Registry.<sup>8</sup> Since then, increased use of new biotherapies has modified the therapeutic panorama, but in the meanwhile focused publications on SSc,<sup>9-12</sup> MS<sup>13</sup> and SLE<sup>14-16</sup> have provided encouraging results from pilot trials using single disease response criteria.

We were, therefore, interested to learn more about the longer term outcome of the originally reported patients. In

addition, we included newly recruited cases and analyzed the determinants of the observed responses after a first autologous HSCT.

## Design and Methods

This was an observational study by the EBMT Working Party on Autoimmune Diseases. Data were collected by questionnaire or by the electronic EBMT data management system ProMISE ([www.ebmt.org](http://www.ebmt.org)) and updated annually. The study was approved by the review boards of all 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, data from 67% of patients alive were updated in 2007. All EBMT participating centers 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 centers ([www.jacie.org](http://www.jacie.org)). The methodology used for data collection according to each disease category and the activity index used for determining that patients had progressed were the same as those described in the report by Gratwohl.<sup>8</sup> All consecutive patients with autoimmune diseases reported to the EBMT registry database from 1996 to December 2007 were included in this study, which was conducted according to the STOBE principles.<sup>15</sup>

### Hematopoietic stem cell transplantation procedures

Standard techniques, as used in autologous HSCT for hematologic malignancies were employed, using either bone marrow, peripheral blood stem cells or both stem cell products. Peripheral blood stem cells were used as the source of stem cells for the majority of the patients (93%) and in most cases were mobilized with cyclophosphamide (1.5-4 g/m<sup>2</sup>) in combination with granulocyte-colony stimulating factor (G-CSF), or with G-CSF alone according to local protocols. *In vitro* purging before autologous HSCT (44%) was performed according to local protocols, using either CD34<sup>+</sup>-positive selection (92%) or by negative purging of lymphocyte subsets by monoclonal antibodies, particularly anti-CD52 (CAMPATH 1), anti-CD3, anti-CD19, or anti-CD20 (8%). The conditioning regimen consisted of either total body irradiation (TBI) (7%) or various combinations of chemotherapy alone (93%), including combinations based on cyclophosphamide (at 150 or 200 mg/kg total dose) (52%), busulfan (4%), and BEAM (carmustine, cytarabine, melphalan, and etoposide) (34%). Antithymocyte globulin was used in 55% of the patients. In order to analyze the effect of the various conditioning regimens on outcomes, the regimens were subgrouped, as done previously, into: (i) high intensity regimens, including any busulfan- or TBI-containing regimens; (ii) low intensity regimens restricted to cyclophosphamide alone, melphalan alone and fludarabine-based regimens; and (iii) intermediate regimens, including all the other combinations. The experience of the center was based on the number of autologous transplants for autoimmune diseases carried out per center during the studied period.

### Statistical analysis

Progression-free survival was defined as survival without evidence of relapse or progression. Progression was considered as any increase of disease activity index<sup>8</sup> as compared to baseline. Overall survival was defined as time to death, irrespective of the cause. The 100-day transplant-related mortality was defined as death

without relapse or progression of autoimmune disease. Cumulative incidence curves were used for 100-day transplant-related mortality<sup>16,17</sup> and compared using the Gray's test as a competing event.<sup>16</sup> Probabilities of progression-free survival 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 patients', disease and graft characteristics with outcomes were evaluated in multivariate analyses, using a Cox proportional hazards model for progression-free survival. 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, USA) 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 the treatment of a severe autoimmune disease in 172 institutions in 27 countries. Most of the autoimmune diseases were rheumatological (60%) or neurological (33%) in nature, whereas HIC and the most recently reported inflammatory bowel disease accounted for a small proportion of cases. The six major groups of autoimmune diseases for which HSCT was performed were MS (n=345), SSc (n=175), RA (n=89), SLE (n=85), JIA (n=65), and HIC (n=37); 104 patients underwent HSCT for other autoimmune indications. Nine patients received a second autologous HSCT (Table 1).

### Transplant activity

There were significant changes in the indications over time. RA has virtually ceased to be an indication for autologous HSCT since 2001 due to the availability of new biological agents. This accounted for a drop in overall transplant activity, although more than 50 autologous HSCT for autoimmune diseases continue to be performed per year (Table 1). Differences in patients' characteristics and in treatment variables according to the original autoimmune diseases were also noticeable (Table 2). Patients with SSc and RA were older than the median of 35 years. As expected, the percentage of females was higher among patients with RA (73%), SSc (71%) and SLE (86%) than among patients with other autoimmune diseases. Disease duration before autologous HSCT varied widely between the major categories of autoimmune disease and the median interval between diagnosis and HSCT was shorter for patients with SSc (30 months) and much longer for those with RA (86 months) and MS (77 months).

### Outcomes

In the whole population, the 5-year overall survival was 85% (95% CI: 79-83%) (Figure 1A), the progression-free survival was 43% (95% CI: 39-47%) (Figure 1B) and the 100-day transplant-related mortality was 5% (95% CI: 3-7%). The causes of death are summarized 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%) from transplant-related causes (Table 3). Infections (45.7%) were the leading cause of transplant-related mortality. Death due to cardiac toxicity (8.4%) was not related to a specific type of conditioning. As shown in Table 4A, the 100-day transplant-related mortality was 2% for MS, 6% for SSc, 1% for RA, 11% for SLE, 11% for JIA and 8% for HIC, with a statistical difference depending on type of autoimmune disease (*P*<0.001).

Five years after HSCT, the progression-free survival 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 SLE, 52% (95% CI: 38-66%) for JIA and 34% (95% CI: 16-52%) for HIC, while the 5-year overall survival 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, with a statistically significant difference depending primarily on the type of autoimmune disease (*P*<0.0001).

### Factors associated with outcome

The results of the univariate and multivariate analysis of prognostic factors are summarized in Table 4a and 4b, respectively, for 100-day transplant-related mortality, progression-free survival and overall survival.

In multivariate analysis, the 100-day transplant-related mortality varied according to the original diagnosis (*P*=0.003) and was lower in experienced centers (*P*=0.003). In addition to the influence of original diagnosis (*P*=0.0007), age less than 35 years (*P*=0.004) and HSCT performed after December 2000 (*P*=0.0015) were associated with a higher progression-free survival (Table 4b).

The original diagnosis (*P*=0.0005) was a strong determinant of overall survival; other factors associated with a

**Table 1.** Overall and yearly activity of autologous HSCT for all cases of severe autoimmune diseases (n=900) reported to the 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
<b>Total</b>	<b>345</b>	<b>175</b>	<b>89</b>	<b>85</b>	<b>65</b>	<b>37</b>	<b>104</b>	<b>900</b>

better overall survival were the centers' experience ( $P < 0.0001$ ), the use of peripheral blood stem cells ( $P < 0.005$ ), age less than 35 years ( $P = 0.01$ ) and a disease duration longer than the median before HSCT ( $P = 0.06$ ) (Table 4b).

## Discussion

The aim of this study was to merge the longer term follow-up data of the 473 patients previously reported by the EBMT in 2003<sup>8</sup> with data from cases reported to the Registry thereafter, in order to analyze the determinants of the clinical responses in 900 patients with severe autoimmune diseases treated with a first autologous HSCT. This is the largest series analyzed worldwide so far. Our data confirm that autologous HSCT is a valid therapeutic option for patients with an autoimmune disease that is progressing despite standard therapy.<sup>2,3,20</sup>

Data were obtained from the EBMT registry using a

large international network after 10 years of an EBMT-EULAR collaboration, including 549 member centers. Free and voluntary data reporting, in accordance with the EBMT rules ([www.ebmt.org](http://www.ebmt.org)), was highly encouraged in the initial consensus.<sup>3</sup> Teams used different transplant techniques, but most of the EBMT participating centers adhered to the broad indications and optimum treatment methods described early in the program,<sup>3,4</sup> whose basic principles are still valid. All centers were subjected to random audits, as part of EBMT audits, to control the consistency of reported data.

All registry data analyses have some limitations.<sup>17</sup> One drawback of our analysis was the missing values concerning the details of conditioning chemotherapy protocols, when TBI was not used. However, the high number of procedures reported to the EBMT registry allowed careful stratification for the analysis of outcomes for each type of autoimmune disease.<sup>17,18</sup> Autologous HSCT has been performed for several major indications since 1996, namely:

**Table 2.** Patients (n=900) with severe autoimmune diseases and graft characteristics at time of first autologous HSCT as reported to the EBMT registry from 1996 to December 2007.

	MS	SSc	RA	SLE	JIA	HIC	Others	Total
N. of autologous HSCT	345	175	89	85	65	37	104	900
N (%) of females	210 (61%)	123 (71%)	65 (73%)	73 (86%)	32 (49%)	19 (51%)	56 (54%)	578 (64%)
Age at Tx (years)	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 (months)	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 (months)	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 hematopoietic stem cells								
Bone marrow	16	4	1	11	29	2	2	65
PBSC ± bone marrow	326 (95%)	168 (98%)	88 (99%)	74 (87%)	36 (55%)	35 (95%)	100 (98%)	827 (93%)
Missing	3	3	0	0	0	0	2	8
Purging								
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 regimen								
Total body irradiation	16	4	1	13	24	2	2	62
Cyclophosphamide alone	8	60	47	6	3	4	11	139
Cyclophosphamide + other	25	49	7	18	15	11	16	141
Melphalan alone	2	2	0	3	0	5	13	25
Fluradabine-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 chemotherapy	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

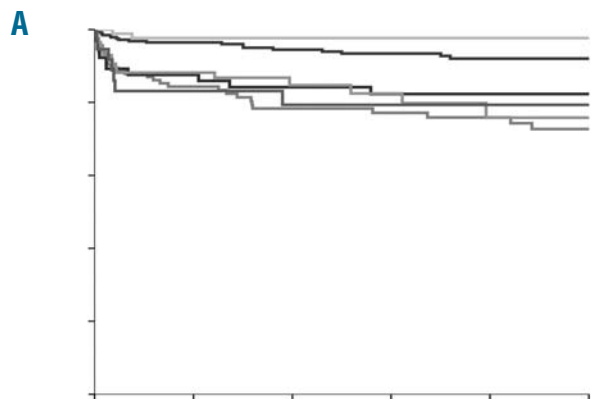
N: number; Tx: autologous HSCT; EBMT: European Group for Blood and Marrow Transplantation; PBSC: peripheral blood stem cells; BEAM: carmustine, cytarabine, melphalan and etoposide.

MS,<sup>13,21,22</sup> SSc,<sup>9,12</sup> RA,<sup>20,25</sup> SLE,<sup>13-16</sup> JIA,<sup>23,24</sup> and HIC<sup>26</sup> and as the experience grew, other indications were added.<sup>27,28</sup> Evaluation of efficacy is not always simple and varies according to the type of autoimmune disease. In MS, which was the most frequent indication for HSCT, progressive disability can be related to the neuro-degeneration, which is part of the most advanced (secondary progressive) phase of the disease.<sup>21,22</sup> For rheumatological and hematologic diseases, progression is usually associated with relapse of inflammatory activity. However, the 5-year progression-free survival of 43% may be a good indicator of the overall outcome of patients with severe autoimmune diseases refractory to standard therapies

who undergo autologous HSCT.

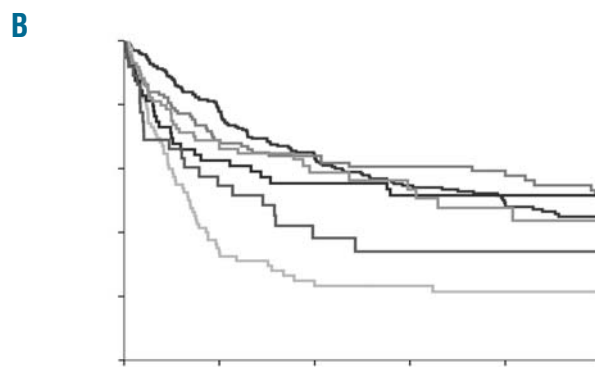
The progression-free survival varied according to the type of autoimmune disease. In the majority of RA patients, the effect of autologous HSCT was rather limited. Indeed, the introduction of new, targeted biological treatments has modified the therapeutic panorama in the past few years with a decrease in the use of transplantation for inflammatory arthritis due to wider use and efficacy of anti-tumor necrosis factor drugs,<sup>20</sup> while the standard treatment of SSc has not improved significantly in the last 10 years for poor prognosis patient.<sup>29</sup> These factors contributed to changes in the distribution of the type of autoimmune disease for which autologous HSCT has been used since 2000. SSc and HIC patients were referred to autologous HSCT rather earlier than RA, MS and SLE patients, illustrating the heterogeneity of each autoimmune disease category before patients are considered refractory to standard therapy. Although the effect of age on the outcome could also be related in part to the type of autoimmune disease, multivariate analysis revealed that the progression-free survival improved in patients under 35 years of age. Indeed, differences in the spontaneous evolution of each type of autoimmune disease 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 patients with severe RA and MS selected for autologous HSCT, the spontaneous progression of the disease evolves towards extensive disability at 10 years, with patients having a life expectancy 5 to 10 years shorter than that of normal controls.<sup>30</sup> On the other hand, intrinsic immunodepression in SLE<sup>1</sup> and major vital organ involvement present in patients



Number of patients at risk

MS	345	220	182	155	122	94
SSc	175	109	88	73	56	46
RA	89	73	51	36	32	29
SLE	85	68	41	32	19	16
JIA	65	52	47	43	37	34
HIC	37	28	21	20	16	15



Number of patients at risk

MS	345	182	128	96	69	49
SSc	175	90	71	57	44	34
RA	89	26	14	13	12	12
SLE	85	50	27	19	12	10
JIA	65	36	30	26	21	19
HIC	37	19	10	8	7	7

**Figure 1.** Kaplan-Meier curves for (A) overall survival and (B) progression-free survival of patients after autologous HSCT for severe autoimmune diseases depending on the disease type, as reported to the EBMT database from 1996 to 2007 (n=900 patients).

**Table 3.** Causes of death after autologous HSCT for severe autoimmune disease in 900 treated patients as reported to the EBMT database 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

\*After failure of autologous HSCT, the patient was treated with allogeneic HSCT and eventually died from graft-versus-host disease. \*\*The five secondary malignancies were: acute myeloid leukemia (MS), bronchial carcinoma (SSc), esophageal carcinoma (SSc), refractory anemia with excess of blasts (SLE) and post-transplant lymphoproliferative disease (others: mixed connective tissue disease).

with severe SLE or SSc significantly impair these patients' spontaneous survival, which was estimated to be between 30% and 50% at 5 years for SSc<sup>31</sup> and between 75% and 80% at 10 years for SLE.<sup>32</sup> In the overall EBMT registry

population, the transplant-related mortality (5%) has clearly improved since the earlier reports on a smaller number of patients in 2001 (12%).<sup>9</sup> Among patients with SSc, there were more deaths from the original disease than

**Table 4A.** Univariate analysis of prognostic factors in 900 patients with severe autoimmune diseases treated by autologous HSCT and reported to the EBMT data base from 1996 to December 2007.

	100-day transplant-related mortality (95% CI)	3-year progression-free survival (95% CI)	3-year overall survival (95% CI)
<b>Category of autoimmune disease</b>			
Multiple sclerosis	2 (0-4)	55 (49-61)	93 (89-97)
Systemic sclerosis	6 (2-10)	63 (55-71)	80 (66-94)
Rheumatoid arthritis	1 (0-3)	23 (13-33)	98 (94-100)
Systemic lupus erythematosus	11 (5-17)	54 (42-66)	87 (79-95)
Juvenile idiopathic arthritis	11 (6-22)	52 (38-66)	82 (72-92)
Hematologic immune cytopenia	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
<b>Patients' age</b>			
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
<b>Sex</b>			
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
<b>Year of autologous HSCT</b>			
Before 2001	5 (3-7)	43 (37-49)	86 (82-90)
2001 or after	4 (2-6)	59 (53-65)	89 (85-93)
	0.53	<0.0001	0.27
<b>Interval between diagnosis and autologous HSCT</b>			
Less than median	6 (4-8)	55 (49-61)	84 (81-88)
More than median	3 (1-5)	48 (42-54)	90 (86-94)
	0.04	0.58	0.007
<b>Source of stem cells</b>			
Bone marrow	9 (3-15)	47 (33-61)	80 (70-90)
Peripheral blood stem cells	4 (2-6)	51 (47-55)	88 (86-90)
	0.08	0.63	0.07
<b>Conditioning regimen</b>			
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
<b>Total body irradiation</b>			
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
<b>Purging</b>			
No purging	5 (3-7)	51 (45-57)	90 (78-100)
Purging	4 (2-6)	50 (44-56)	86 (82-90)
	0.28	0.37	0.15
<b>Center experience</b>			
N. of patients ≤ 13 (n=441)	7 (5-9)	48 (42-54)	83 (79-87)
N. of patients >13 (n=421)	3 (1-5)	53 (47-59)	92 (90-94)
	0.004	0.45	0.0001

from the transplant procedure, in contrast to the pattern in patients with other diagnoses, reflecting a different disease-related clinical evolution. Fatal infections appeared to be more frequent in patients with SLE than in the other groups of patients (39% *versus* 22%), but the difference was not statistically significant ( $P=0.12$ ). Multivariate analysis revealed an effect of the experience of the center for autologous HSCT in autoimmune diseases, influencing both the 100-day transplant-related mortality and the overall survival. The center gained experience with increased activity, as previously shown in autologous

HSCT for hematologic malignancies.<sup>33</sup> This effect of the transplant center, presumably due to better selection of patients and clinical monitoring during and after the procedures, may contribute to heterogeneous perceptions about the risk-to-benefit ratio of autologous HSCT in autoimmune diseases. In this context, close cooperation between transplant teams and referring specialists is fundamental. The results may be of importance for future decisions on health care policy and support the need for centers with significant levels of activity and resources for adapted clinical care in treating rare autoimmune diseases.<sup>34</sup>

Intensity of the conditioning regimen, need for a myeloablative schedule and graft manipulation have all been extensively discussed in the context of HSCT for autoimmune diseases. In the present study, no significant correlation was found between the intensity of the conditioning regimen and transplant-related mortality, possibly because of the extremely low number and decreasing number of such deaths in recent years. The intensity of conditioning regimen influenced the 3-year progression-free survival in the univariate analysis, but not on multivariate analysis. Graft manipulation was employed in 44% of the reported procedures, largely based on laboratory studies and a hypothetical risk of re-infusion of pathogenic T cells with the graft. This strategy is, however, associated with more severe immunosuppression and might result in greater toxicity. So far, there are no data to support graft manipulation strategies as a mean of improving outcome.<sup>2,3,8,35</sup> In the present study, no significant association was found between graft purging and either transplant-related mortality or progression-free survival. However, this finding is limited by the heterogeneity of the conditioning regimens applied in the two groups (those receiving manipulated or unmanipulated grafts). The value of graft manipulation in the setting of autoimmune diseases is, therefore, still unclear and merits further investigation.

Peripheral blood as the source of stem cells appeared to improve overall survival in multivariate analysis. The main reason for using bone marrow as the source of cells for HSCT in autoimmune diseases is to reduce the number of T cells in the graft. However, evidence that graft T-cell content affects the relapse rate is still lacking and, therefore, the greater safety of using peripheral blood stem cells is to be preferred. A few studies reported safety and short-term efficacy of high dose cyclophosphamide alone for treating SLE and MS,<sup>36</sup> 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 mobilization, followed by conditioning and stem cell infusion both aim at resetting the autoimmune response and inducing long-term tolerance via fundamental changes of the immune system.<sup>37,38</sup> Indeed, several translational studies have shown that clinical improvements after HSCT in patients with SSs,<sup>39</sup> MS,<sup>40</sup> JIA,<sup>41</sup> and SLE<sup>42</sup> patients can be associated with drastic reactivation of thymic activity, including the restoration of a new polyclonal T-cell repertoire<sup>39-41</sup> and *de novo* induction of thymus-derived natural Treg cells<sup>40,41</sup> which are essential for restoration of peripheral tolerance for autoantigens, or with the elimination of autoantibody-producing cells.<sup>42</sup>

**Table 4B. Multivariate analysis of prognostic factors in 900 patients with severe autoimmune diseases treated by autologous HSCT and reported to the EBMT database from 1996 to December 2007. Only statistically significant variables are reported.**

100-day transplant-related mortality*	P	HR	95.0% CI
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
Rheumatoid arthritis			
Systemic lupus erythematosus		9.8	1.25-76.8
Juvenile idiopathic arthritis		7	0.81-60.8
Hematologic immune cytopenia		5.23	0.54-50.6
Other		4.01	0.48-33.4
Progression-free survival**			
Age < 35 years	0.004	1.37	1.1-1.7
Year ≥ 2001	0.0015	1.47	1.16-1.86
Diagnosis	0.0007		
Multiple sclerosis		0.86	0.69-1.07
Systemic sclerosis		0.68	0.53-0.87
Rheumatoid arthritis		1	
Systemic lupus erythematosus		0.96	0.72-1.3
Juvenile idiopathic arthritis		0.94	0.66-1.34
Hematologic immune cytopenia		1.22	0.84-1.77
Other		0.97	0.73-1.29
Overall survival			
Age < 35 years	0.01	1.72	1.13-2.62
Diagnosis	0.0005		
Multiple sclerosis		0.65	0.42-1
Systemic sclerosis		1.77	1.19-2.6
Rheumatoid arthritis		1	
Systemic lupus erythematosus		2.06	1.29-3.27
Juvenile idiopathic arthritis		1.17	0.61-2.21
Hematologic immune cytopenia		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 <i>vs.</i> 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 for conditioning regimen; PBSC: peripheral blood stem cells.

The improved progression-free survival since 2000 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 greater than 50 mmHg in SSc,<sup>9,10,12,43</sup> high disability scores in MS,<sup>21,22</sup> and TBI without lung shielding in SSc.<sup>11</sup> Broad diffusion of these findings via international collaborative networks and publication of consensus reports<sup>4,43</sup> were important to the developing use of autologous HSCT in autoimmune diseases. The improved progression-free survival over the years could also be linked to the increased experience of transplant centers and to the drop in autologous HSCT activity for RA.

In conclusion, this follow-up of the report by Gratwohl *et al.*<sup>8</sup> further confirms the value of autologous HSCT in patients with severe autoimmune diseases. The original diagnosis appears to be the most relevant prognostic factor, reflecting the high clinical and biological heterogeneity of these diseases. Importantly, the present study, drawing on data from a larger number of patients with longer follow-up, highlights a new finding: the transplant center is also an independent variable determining transplant-related mortality and overall survival. Better selection and improved clinical management of the patients and effective collaboration between the referring specialists and the transplant teams may underline this finding. The results of this study sum up 10 years of an EBMT-EULAR international collaboration and form the basis for future directions in the field. They strongly support the ongoing European and North American phase III trials in severe autoimmune diseases, aimed at comparing autologous HSCT with standard therapies in SSc (the ASTIS trial; [www.astistrial.com](http://www.astistrial.com) in Europe and the SCOT trial; [www.sclerodermatrial.org](http://www.sclerodermatrial.org) in North-America), MS (ASTIMS, [www.astims.org](http://www.astims.org)), Crohn's disease (ASTIC, [astic@nottingham.ac.uk](mailto:astic@nottingham.ac.uk)) and SLE (ASTIL).

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## Appendix

The following investigators contributed to the Autoimmune Disease' Working Party: Athanasios Fassas, George Papanicolaou General Hospital, Thessaloniki, Greece; Alberto Bosi, Ospedale di Careggi, Firenze, Italy; Andrea Bacigalupo, Ospedale San Martino, Genova, Italy; Roelof Willemze, Leiden University Hospital, Leiden, The Netherlands; Jian Ouyang, The affiliated drum Tower Hospital of Nanjing University Medical School, Nanjing, China; Tomás Kozák, Charles Univ. Prague, Prague, Czech Republic; John Moore, St. Vincent's Hospital, Sydney, Australia; L. Kanz, Universität Tübingen, Tübingen, Germany; Igor A. Lisukov, Institute of Clinical Immunology, Novosibirsk, Russia; Christian Gisselbrecht, Hôpital St. Louis, Paris, France; Enric Carreras, Hospital Clinic, Barcelona, Spain; Mats Brune, Sahlgrenska University Hospital, Goeteborg, Sweden; Marino Andolina, Istituto per l'Infanzia 'Burlo Garofolo', Trieste, Italy; Eefke Petersen, University Medical Centre, Utrecht, The Netherlands; Anton Schattenberg, Radboud University-Nijmegen Medical Centre, Nijmegen, The Netherlands; Boris Afanasyev, SPb State I. Pavlov Medical University, St. Petersburg, Russia; Jan Cornelissen, Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands; Gordon Cook, St James's Institute of Oncology, Leeds, United Kingdom; Gunnar Oberg, University Hospital, Uppsala, Sweden; Fabio Ciceri, San Raffaele Scientific Institute, Milano, Italy.

## Authorship and Disclosures

DF: concept of the study, methodology, data acquisition and interpretation, and manuscript writing; ML: statistical analysis of the data and results section; AT: concept of the study, data collection, and writing sections of the manuscript; AF, GLM and JO: multiple sclerosis analysis; JVL: preparation of the manuscript; TK: methods and findings sections; JM: study design and coordination, and contributed to writing the manuscript; IK: treatment of patients, data acquisition and final corrections; VC: data management; AM: introduction and discussion sections; AG: study design, analysis and writing the manuscript; RS: reviewed the whole paper in his position as Chairman of the EBMT Autoimmune Diseases Working Party.

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