

* CHAPTER 32

HSCT for autoimmune diseases in adults

R. Saccardi, D. Farge

1. Introduction

Autoimmune diseases (ADs) are a heterogeneous group of diseases, affecting 10–12% of the population. Consensus indications for the use of HSCT to treat severe ADs were published in 1997 (1). Patients should be considered for HSCT when matching the following criteria:

1. Diagnosed with an AD severe enough to have an increased risk of mortality or advanced and irreversible disability;
2. The ADs must be unresponsive to conventional treatments;
3. HSCT should be undertaken before irreversible organ damage so that significant clinical benefit can be achieved.

The introduction of new biotherapies has modified the therapeutic panorama since 2002, resulting in a drop of activity in HSCT for inflammatory arthritis. Today, more than 1300 patients worldwide have received an HSCT for an AD alone. Autologous HSCT phase II trials showed that in patients with a favourable outcome, a resetting of a dysregulated autoaggressive immune system may occur, rather than simple ablation of auto-reactive cells. Results of allogeneic HSCT are as yet unclear, due to small numbers, and heterogeneous patient groups and treatment regimens. Peripheral blood stem cells (PBSC) have mainly been used, with a the most frequent mobilisation regimen including the combination of cyclophosphamide (Cy) and G-CSF. As ADs are extremely heterogeneous, a comparison of protocols and outcome depends on careful stratification of diagnosis and phases of diseases.

So far in 2007, 841 HSCT procedures have been registered in the European Group for Blood and Marrow Transplantation (EBMT) database (Table 1), the rest being registered in the US International Bone Marrow Transplantation Registry (IBMTR) and in Asia. In the EBMT database, the most commonly transplanted diseases are multiple sclerosis (MS), scleroderma (SSc), rheumatoid arthritis (RA), juvenile arthritis (JIA) and systemic lupus erythematosus (SLE), coming from over 100 transplant centres in more than 20 countries (Table 2). Prevalence of female sex

Table 1: Overview of data on HSCT for ADs reported to the EBMT database (August 2007)

Patients	841
Transplant procedures	863
Centres/countries	171/25
Autografts/allografts	801/40
Age at transplant (yrs)	35
Male/female	313/526

Table 2: Distribution of diagnoses in the EBMT database

Multiple sclerosis	297	Haematological	58
Connective tissue disorders	261	- ITP	21
- SSc	147	- AIHA	12
- SLE	84	- Evan's	9
- PM/DM	12	- Pure red cell	7
- Sjogren	3	- Pure white cell	2
- Other/unknown	15	- Other	7
Arthritis	154	Vasculitis	29
- Rheumatoid arthritis	82	- Behcet's	6
- Juvenile chronic arthritis:		- Wegener's	7
• Systemic JIA	38	- Microscopic polyarteritis nod	3
• Other JIA	19	- Takayasu	2
• Polyarticular JIA	9	- Churg-Strauss	2
- Psoriatic arthritis	3	- Other	9
- Other	3	Other neurological	16
Inflammatory bowel disease	11	- Myasthenia gravis	3
- Crohn's disease	9	- Other	13
- Ulcerative colitis	2	Other/missing	15

PM/DM: polymyositis/dermatomyositis; see text for other abbreviations

and young age reflects the natural distribution of the diseases. Long-lasting responses were obtained in all disease categories with an overall adjusted transplant-related mortality (TRM) being $7\pm 3\%$ at three years, directly related to the type of AID disease (SSc and SLE at higher risk), the year of transplant with a learning curve and the intensity of conditioning (more intensive conditioning had a higher risk of TRM but lower probability of disease progression) (2). In the following paragraphs clinical results and indications for the major ADs will be overviewed. Less common diseases have been reviewed elsewhere (3).

2. Multiple sclerosis

MS is the most frequent diagnosis for which HSCT has been used. In 2006, a retrospective analysis of 183 cases from the EBMT database, of which 99 were secondary progressive forms (SP), 19 primary progressive and 41 relapsing forms (RR), was published (4). Overall, 63% of patients did not progress in their disability after a median follow-up of 42 months. TRM was 5%, mostly concentrated prior to the year 2000. More aggressive regimens, including busulfan or a combination of graft manipulation and serotherapy, resulted in a higher toxicity without any advantage in terms of relapse prevention or disability progression. The most widely-used regimen was the association of BEAM and anti-thymocyte globulin, with an

unmanipulated graft, and among the 53 patients who received this regimen, no TRM was reported. Ideally, rapidly progressing patients should be transplanted in the RR phase, before an advanced disability or a SP form has developed. An ongoing update of this analysis, carried out among patients treated with the BEAM/ATG protocol, confirms the better outcome of RR over SP forms. The ASTIMS trial comparing prospectively HSCT vs. mitoxantrone as control arm is currently ongoing, with 15 patients included so far out of the 30 required to complete the protocol.

3. Systemic sclerosis

Phase I/II pilot studies showed that HSCT was feasible in carefully selected patients with diffuse SSc allowing an improvement of 25% or more in the skin score in 70% of the first 65 treated patients. However, the early TRM was higher than the 3% reported in non ADs patients and varied according to conditioning regimen, using either Cy alone (200 mg/kg total) or 8 Gy radiation plus Cy 120 mg/kg body weight. The initial TRM was 8.6% in the EBMT extended report, which could be reduced to 5.2% when stricter exclusion criteria were applied (mean pulmonary arterial pressure >50 mmHg, severe cardiac involvement or pulmonary fibrosis and uncontrolled systemic hypertension) (5). More importantly, autologous HSCT induced a major regression of SSc dermal fibrosis, confirmed by histological analysis, which had never been previously reported with any other treatment in SSc. Prolonged follow-up of patients confirmed sustained improved functional status, fall in skin score and stabilisation of lung function, whereas death from disease progression was strikingly lower compared to the 5-year mortality rate estimated at 30% in such severe SSc patients (6). These results were the basis for the ongoing ASTIS trial comparing HSCT (Cy, ATG and CD34 selected graft) *versus* monthly intravenous pulse Cy 750 mg/m² for 12 months, with 103 patients included so far out of the 120 planned.

4. Systemic lupus erythematosus

With the aim of suppressing autoimmune disease in one concentrated effort rather than drawn out over a long period, several early European phase I/II trials showed that severe SLE patients refractory to standard therapy responded to HSCT. The first EBMT/EULAR retrospective study of 55 patients, most with either renal and/or CNS involvement, showed that 66% achieved a "remission" with a 12% TRM (due to the selection of patients refractory to all previous therapies) (7). Of those achieving remission after HSCT, 32% subsequently relapsed to some degree, but were then mostly easily controlled on standard agents which were previously ineffective. The safety of HSCT is likely to be improved by better patient selection according to the consensus criteria and better choice of conditioning regimen. In a US single centre

study, 50 patients refractory to standard therapies with either organ- or life-threatening visceral involvement also showed a durable remission after HSCT with a 4% TRM (8). Based on these experiences, the ASTIL phase IIb trial was designed to compare the efficacy of autologous HSCT versus rituximab (anti-CD20) as induction therapy followed by maintenance therapy by mycophenolate mofetil in both arms in the treatment of severe SLE refractory to standard therapy.

5. Arthritis

5.1. Rheumatoid arthritis

Analysis of the first 78 EBMT patients showed significant improvement in 67%, whereas most had failed conventional disease modifying anti-rheumatic drugs (DMARDs) before HSCT. The conditioning regimen in the majority was Cy 200 mg/m² alone after either G-CSF or Cy/G-CSF mobilisation. Only one TRM from sepsis was reported five months after higher intensity conditioning (busulfan/Cy). Some degree of relapse was seen in 73% of patients, but was relatively easy to control with drugs which had been ineffective pre-transplant. In the past ten years, TNF blockers have emerged as safe and highly effective treatments for resistant RA, although 25% of treatment failures remain. The use of autologous HSCT as a salvage therapy is now limited to these rare patients who will also be candidates for other new biotherapies.

5.2. Phase I/II juvenile idiopathic arthritis

The use of anti-TNF and anti-IL-6 receptor treatments for DMARD-resistant JIA has proven of great value, but some children still remain resistant with severe morbidity, impaired quality of life and increased mortality rate. In the EBMT database 66 children, most of whom had with Still's disease, were treated by autologous HSCT using stem cells obtained from the bone marrow and a conditioning protocol of Cy 200 mg/kg body weight, TBI 4Gy and ATG. Impressive results showed a prolonged drug-free follow-up of 6–60 months. In a report of 34 patients (9), 18 entered complete and 6 partial drug-free remissions, for whom the corticosteroid dose could be reduced or stopped with subsequent restoration of growth. Four patients died, 3 from the macrophage activation syndrome, a well-known complication of systemic JIA, thought to be related to intercurrent infection or uncontrolled systemic activity of the disease at the time of transplantation. Since then protocols have been modified, to control systemic activity before HSCT with methyl-prednisolone, and no further such deaths have occurred. The results of phase I/II trials in JIA using Cy alone versus Cy and TBI suggested no advantage of the TBI.

6. Crohn's disease

Several cases with satisfactory results have been reported, and guidelines for considering HSCT in Crohn's disease have been published. In Europe, the ongoing phase IIb ASTIC trial (Table 3) is evaluating the potential clinical benefit of haematopoietic stem cell mobilisation followed by immediate versus delayed HSCT in patients with relapsing Crohn's disease and clear intolerance or toxicity to a conventional treatment protocol.

Table 3: EBMT ongoing prospective trials for ADs

Disease	Trial Design	Acronym	Status	Website
SSc	Autologous HSCT vs. monthly Cy	ASTIS	Started 2002 103/120	www.astistrial.com
MS	Autologous HSCT vs. monthly mitoxantrone	ASTIMS	Started 2004 15/30	www.astims.org
Crohn's	Mobilisation followed by early vs. late autologous HSCT	ASTIC	Launch Q1 2007	www.astic.eu
SLE	Autologous HSCT vs. anti-CD20 MoAb	ASTIL	Planning Q1 2008	pending

Numbers in status box indicate patients enrolled/patients planned

7. Haematological cytopenias

In this group of patients, a relatively higher proportion of allogeneic transplantation was reported, showing encouraging results in terms of relapse-free outcome. Most of the patients who received an autologous HSCT were treated with a Cy-based conditioning regimen, showing a sustained response in 33% of the cases reported to the EBMT database (10).

8. Conclusions

The main indications for HSCT among ADs are MS and SSc, in which a significant subset of patients still shows an unsatisfactory response to both conventional and new immunomodulating treatments. Initial experience has been used to design several ongoing prospective, phase IIb-III randomised trials both in Europe and United States, to compare HSCT with conventional, approved treatment. Inclusion of patients in such institutional trials is encouraged.

Acknowledgments

The Authors are gratefully indebted to Virginie Chesnel for her helpful assistance in the data management.

References

1. Tyndall A, Gratwohl. A Blood and marrow stem cell transplants in auto-immune disease: A consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1997; 19: 643-645.
2. Gratwohl A, Passweg J, Bocelli-Tyndall C, et al. Autologous haematopoietic stem cell transplantation for autoimmune diseases. *Bone Marrow Transplant* 2005; 35: 869-895.
3. Kapoor S, Wilson AG, Sharrack B, et Al. Haemopoietic stem cell transplantation – An evolving treatment for severe autoimmune and inflammatory diseases in rheumatology, neurology and gastroenterology. *Hematology* 2007; 12: 179-191.
4. Saccardi R, Kozac T, Bocelli-Tyndall C, et al. Autologous stem cell transplantation for progressive multiple sclerosis: Update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. *Mult Scler* 2006; 12: 814-823.
5. Farge D, Passweg J, van Laar JM, et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: Report from the EBMT/EULAR Registry. *Ann Rheum Dis* 2004; 63: 974-981.
6. Vonk MC, Marjanovic Z, van den Hoogen FH, et al. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. *Ann Rheum Dis*, Epub 2007 May 25: 98-104.
7. Jayne D, Passweg J, Marmont A, Farge D, et al. Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* 2004; 13: 168-176.
8. Burt RK, Traynor A, Statkute L, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* 2006; 295: 559-560.
9. Wulfraat NM, Sanders EA, Kamphuis SS, et al. Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. *Arthritis Rheum* 2001; 44: 728-731.
10. Passweg JR, Rabusin M, Musso M, et al. Haematopoietic stem cell transplantation for refractory autoimmune cytopenia. *Br J Haematol* 2004; 125: 749-755.

Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. How many patients have received HSCT for an autoimmune disease in the past ten years?

- a) 100–500 patients

- b) 500–1000 patients
- c) 1000–3000 patients
- d) More than 3000 patients

2. Which are the main indications for HSCT among ADs?

- a) Autoimmune cytopenia
- b) Rheumatoid arthritis
- c) Systemic lupus erythematosus and vasculitis
- d) Systemic sclerosis and multiple sclerosis

3. Which is the current transplant related mortality in autologous SCT for AD?

- a) < 1%
- b) 3–10%
- c) 10–20%
- d) 20–30%

4. Which of the following criteria is *not* an indication for HSCT?

- a) Patients diagnosed with an AD severe enough to have an increased risk of mortality or advanced and irreversible disability
- b) ADs not responsive to conventional treatment
- c) Young patients at diagnosis
- d) Advanced disease without irreversible severe organ damage

5. Which the prevalent source of HSCs for transplantation in ADs?

- a) PBSCs mobilised by cyclophosphamide and G-CSF
- b) PBSCs mobilised by G-CSF alone
- c) Bone marrow
- d) Cord blood