

## Stem cell transplantation in rheumatoid arthritis

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### Abstract

The therapeutic potential of high dose cytotoxic therapy and stem cell transplantation (SCT) in severe rheumatoid arthritis (RA) was originally supported by animal studies and serendipitous clinical cases where allogeneic and autologous procedures were shown to ameliorate and potentially cure the disease. Phase I and Phase II clinical studies established the feasibility, safety and efficacy of autologous stem cell mobilisation and transplantation. Although it was clear that the effects of high dose chemotherapy and autologous SCT could safely achieve profound responses, sustained control of disease usually required the reintroduction of disease modifying agents. Responses were improved with dose escalation of the conditioning regimen, and also with post-SCT therapy, such as rituximab, but were not observed with graft manipulation. Phase III studies were attempted, but recruitment was compromised by the increasingly widespread use of biological anti-rheumatic agents. Autologous SCT is now only reasonably considered in relatively rare patients whose disease has resisted conventional and biological treatments, and small numbers of cases continue to be registered with the EBMT. Occasional patients treated with allogeneic and syngeneic SCT continue to stimulate academic interest, particularly as some appear to be cured, but significant logistical and toxicity issues mean that routine and widespread application is unrealistic. In summary, SCT continues to have a limited therapeutic potential in rare patients with RA refractory to modern therapy and sufficient fitness for the procedure. From a scientific perspective, ablation of the dysfunctional rheumatoid immune system and its reconstruction with SCT has provided useful insights into the pathophysiology of RA.

**Keywords:** *Rheumatoid arthritis, stem cells, bone marrow, haemopoietic transplantation*

### Introduction

A decade ago rheumatoid arthritis (RA) was considered an attractive candidate disease in which to study stem cell transplantation (SCT). It was (and still is) the most common systemic autoimmune disease, and although, not immediately life-threatening in most cases, was a cause of significant long-term morbidity, shortened lifespan and significant economic costs [1]. In addition, from a transplant viewpoint, it was possible to select severely affected patients with good vital organ function who, compared with other systemic autoimmune disorders, would be expected to tolerate the procedure well. Finally, it was easy to assess subjective and objective responses to treatment quickly, and

non-invasively, in contrast to some other autoimmune diseases where more invasive or expensive assessments are necessary [2].

It was with these principles that a number of centres, principally in Australia, the Netherlands, UK, and USA embarked upon a number of studies in humans to define the potential therapeutic role of mainly autologous, but also syngeneic and allogeneic SCT in RA [3,4]. Transplantation was one of several new therapeutic strategies for the treatment of severe RA and at around the same time period, several other competing therapies, notably the anti-TNF drugs, and rituximab, were undergoing evaluation [5].

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## Pre-clinical studies

### Animal data

The background for commencing human studies of SCT in RA was provided by animal studies. Early studies focussed on allogeneic and syngeneic transplantation, which demonstrated cure of disease [6]. However, and perhaps surprisingly, a high incidence of remission was observed following autologous or pseudoautologous BMT in *Mycobacterium tuberculosis* induced adjuvant arthritis [7]. Timing of relapse could be reduced by transplanting earlier in the course of disease [8] and by higher doses of total body irradiation (TBI) [9], although, chemical conditioning regimens were shown to be equivalent to myeloablative TBI [9]. Neither T-cell depletion nor addition of autologous splenocytes to the autografts appeared to make any difference on the likelihood of relapse [7,10]. It was hypothesised that efficacy of SCT is due to ablation of self-reactive lymphocytes during conditioning followed by induction of self-tolerance by re-education of HSC-derived lymphocytes. Other animal models provided further evidence in support of SCT as a potential treatment for RA (Table I).

### Human data

Additional evidence for SCT in the treatment of RA was provided by reports of patients with RA who had received SCT primarily for the conventional indications of malignancy or severe aplastic anaemia. These “serendipitous” cases were heterogenous with regards to the conditioning regimen, frequency of graft manipulation, method of graft-versus-host disease (GVHD) prophylaxis and robustness of response evaluation (Table II).

It appears that cure of RA is possible with “serendipitous” allogeneic SCT. However, cure is not

universal as demonstrated by the early relapse of the case of McKendry et al. [16]. The reasons for some patients being cured and others not are uncertain, and clearly numbers are small. However, one notable observation from these reports was that long term remissions/cure appear to be associated with GVHD, supportive of a clinically significant graft-versus-autoimmune effect [14]. Interestingly, in contrast to some other autoimmune diseases, there are no documented cases where RA has been transferred from SCT donors with active to recipients, despite such procedures having been performed [17].

In contrast to allogeneic SCT, cases of RA receiving autologous SCT for malignancy were not so strongly associated with long-term remissions, although, significant amelioration of disease was observed (Table III). However, allogeneic SCT was generally considered too high risk to consider in patients with a non-immediately life threatening disease such as RA. Although, cure seemed unlikely with autologous SCT, its toxicity profile was considered acceptable to investigate it as a means of intensive disease control in patients, where other treatment options had failed. In the era before biological therapies became widely available, disease modifying anti-rheumatic drug (DMARD) resistant patients were relatively numerous.

## Autologous SCT

The first clinical trials of the safety and efficacy of autologous SCT in patients with severe RA were conducted mainly in Australia, USA, the Netherlands, and UK [21–26]. Numerous case reports and small series have been published [4]. In addition, clinical studies have also confirmed the feasibility of peripheral blood stem cell (PBSC) mobilisation in patients with severe RA, with a documented risk of disease

Table I. Studies of BMT in animal arthritis.

Animal	Model	Type of BMT	Conditioning	Response
Buffalo rat [6]	Induced with <i>M. tuberculosis</i>	Allogeneic/syngeneic	TBI	Regression
Buffalo rat [7]	Induced with <i>M. tuberculosis</i>	Autologous/pseudoautologous	TBI	Regression
DBA/1J mouse [11]	Induced with collagen	Allogeneic	TBI	Regression
NZB/KN mouse [12]	Spontaneous	Allogeneic	TBI	Prevention

Table II. Outcomes of RA following treatment with sibling allogeneic BMT for aplastic anaemia.

Pre-BMT conditioning therapy	Post BMT immuno-suppression	GVHD	RA Remission
Cy 200 mg/kg [13]	Methotrexate, ATG	Acute and chronic	> 20 years
Cy 200 mg/kg [14,15]	Ciclosporine, steroids	Acute and chronic	> 20 years
Cy 200 mg/kg [14,15]	Ciclosporine A, steroids	Acute and chronic	> 20 years
Cy 200 mg/kg [14]	Ciclosporine	Chronic	2 years, DMARD treatment then remission > 11 years
Cy 200 mg/kg, TBI 4 Gy, prednisolone 400 mg [16]	Methotrexate, steroids	Nil	2 years then progressive disease

Table III. Outcome of RA post autologous SCT for lymphoma.

Conditioning	Outcome
BEAM [17]	Remission > 19 months
BEAM [18]	Relapse 20 months
BuCy [19]	Relapse 5 weeks

flare, if G-CSF is used without cyclophosphamide priming [27,28].

Most of the world's cases were analysed together in a joint European Group for Blood and Marrow (EBMT) and Autologous Bone Marrow Transplant Registry (ABMTR) registry analysis of 73 patients from 15 centres [29]. In this retrospective study, patients had been treated previously with a mean of five DMARDs and most patients had been treated prior to the introduction of biological agents. Only four patients had failed on anti TNF treatment. Most of the patients received conditioning with high dose cyclophosphamide (mainly 200 mg/kg) with or without anti-thymocyte globulin (ATG). Most patients were rescued with unmanipulated autologous peripheral blood stem cells. There was no documented transplant related mortality.

Response to SCT was reported using the American College of Rheumatology (ACR) criteria. Most patients had persistent or relapse of disease activity within 6 months of transplant and started back on DMARD therapy, which provided control in approximately half the patients, even though, it was the same as previously used in many patients. The combination of SCT and reintroduction of new or previously used DMARD treatment resulted in disease control in most patients, with 67% of patients sustaining an ACR 50 response out to 18 months. Patients with seronegative RA had a significantly better response than those with seropositive disease. Significant improvements in disability and tender joint counts in this group of patients are summarised in Figure 1 (Table IV).

Encouraged by the early results of autologous SCT in RA, the EBMT Working Party set up the Autologous Stem-Cell Transplantation International Rheumatoid Arthritis (ASTIRA) trial. This phase III study aimed to evaluate the role of autologous transplant followed by maintenance methotrexate in patients with severe active and anti-TNF resistant RA. However, in the post millennium era of widespread use of anti-TNF and other biological therapies, recruitment was limited, and the trial was ultimately closed [4,29,30].

Despite the lack of success in completing a large phase III study [31], other clinical and laboratory studies have been completed which have added to the concept of autologous SCT as a means of disease control. To resolve whether T-cell dose in the reinfused autograft was important factor, a randomised

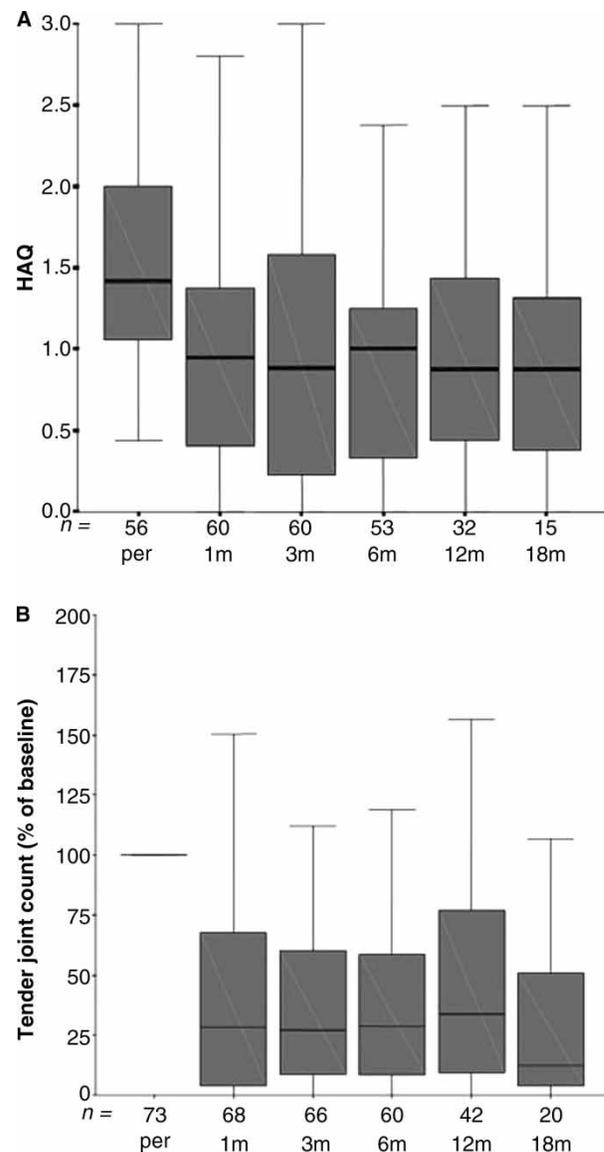


Figure 1. Response in terms of disability by HAQ score [(A) with  $p < 0.005$  at all time points] and relative reduction in tender joint count [(B), with  $p = 0.0001$  at all time points] in the EBMT/ABMTR analysis. It is emphasised that responses follow autologous SCT and, in the majority of cases, the subsequent reintroduction of DMARDs. Reproduced with permission from J Rheumatol (<http://www.jrheum.com>).

controlled trial of CD34 selected versus unselected grafts following treatment with high dose cyclophosphamide 200 mg/kg was conducted between several Australian centres [32]. In keeping with the retrospective registry analysis [24], the study provided no support for the use of CD34 selection as a means of depleting T cells and other immune effectors, at least for this dose of conditioning. It remains the only randomised comparison of graft manipulation (and the only published randomised trial in the field as a whole).

Although, it was clear from clinical and laboratory data that autologous SCT had a sustained anti-inflammatory effect on active synovitis, there

Table IV. Larger clinical studies evaluating autologous HSCT for severe RA.

Reference	No. of patients	Conditioning regimen	Graft manipulation	Response	Time to relapse
[21]	4	Cy 100 mg/kg	None	4/4	3–4 months in 4/4
	4	Cy 200 mg/kg	None	4/4	3–19 months in 3/4
[22]	4	Cy 200 mg/kg + ATG + TBI (1)	Positive CD34 + selection	4/4	3–9 months in 4/4 Further remission maintained at 9 and 20 months in 2/4
[24]	14	Cy 200 mg/kg	Positive CD34 + selection	7/10	–
[29]	18	Cy 200 mg/kg	Positive CD34 + selection	70% no difference between groups	Median 147 d
	15	Cy 200 mg/kg	None		Median 180 d 4/33 maintained remission at 11–17 months
[28]	76	Cy 200 mg/kg (62), various	T-cell depletion (45); Unmanipulated (28)	67% at least ACR50%	Most restarted DMARDs within 6 months

Data from many of the patients reported in the smaller studies were included in the EBMT/ABMTR report; Cy, cyclophosphamide, ATG, anti-thymocyte globulin; TBI, total body irradiation; Bu, busulfan; and ACR, American College of Rheumatology

remained a question of whether the procedure had any effect on reducing joint erosion. The Leiden group studied eight patients prior to and at 1 and 2 years, following transplant and they were able to establish that there was significant reduction in the progression of joint damage [33].

The same group completed a study of long term health status in eight patients with over 5 years follow-up post SCT. They found that general and disease specific health status parameters improved in the first 2 years post SCT, which translated into a gain of 0.28 Quality Adjusted Life Years (QALYs) of health benefit over baseline measurements. Ultimately, health status returned to baseline levels within 2–5 years. Nevertheless, this study suggested that, provided treatment related mortality was less than 2.8%, autologous transplantation could yield more QALYs than conventional treatment. Given that registry data supports a significantly lower risk of TRM, the authors considered autologous SCT a realistic treatment option in patients with severe RA [34]. The findings of this study were also in line with earlier studies that autologous SCT would be an acceptable treatment option to patients, if TRM was less than 2% [35].

The authors suggested that the way ahead would be to prolong the initial benefit of the autologous SCT by introducing new therapies without increasing the treatment related mortality. This has not been widely trailed, but the best evidence for this being a potentially effective approach is provided by Moore and colleagues [36] in which patients relapsing post SCT were systematically treated with rituximab, which was highly effective at controlling disease.

Studies have also examined the composition of rheumatoid synovium before and after autologous SCT. One study showed that clinical improvement is associated with reduction of macroscopic and

microscopic synovitis [37]. Low-level inflammation may persist despite this treatment and eventually clinical relapse occurs in association with associated with a re-invasion of the synovium with CD4 cells, despite ongoing peripheral blood CD4 depletion. Another study showed that clinical responders had greater baseline expression of synovial T-cell markers than non-responders [38]. SCT resulted in profound but incomplete immunoablation of both the memory and naïve T-cell compartment. Remissions and relapses in responders subsequently paralleled reduction and re-expression, respectively, of these markers. A further study investigated immune recovery in RA patients post-SCT and compared them to patients undergoing the SCT for malignancy. Interestingly, the procedure rendered the RA patients lymphopenic for longer than the controls. The delay in recovery was associated with a failure to expand peripheral T cells, possibly related to a relative deficiency of interleukin-7 [39].

### Syngeneic SCT

Two patients have undergone syngeneic SCT specifically for severe RA. The first patient, treated in Melbourne, had severe refractory seronegative RA. He received treatment with cyclophosphamide 200 mg/kg and ATG followed by G-CSF mobilised PBSC from his genetically identical twin brother. At 6 weeks, he had achieved remission and has been in clinical and laboratory remission for over 9 years. The authors demonstrated apparent adoption of the syngeneic donor immune system, which may have been significant in the probable cure of disease ([40,41] and personal communication, Dr Jeff Szer).

In contrast, a second patient, a 44-year-old lady with progressively erosive, seropositive RA received

high dose cyclophosphamide (but not ATG) and a syngeneic graft. She had a flare of her RA at 1 month post SCT, requiring treatment with DMARDs, and continued to have active disease associated with a synovial inflammatory infiltrate, notably of plasma cells [42].

### Allogeneic SCT

There has been one report of allogeneic SCT for severe RA. A 52-year-old lady, who was refractory to treatment with autologous SCT and DMARD therapy, including anti-TNF drugs, went on to have a non-myeloablative allogeneic SCT from an HLA-matched sibling, following conditioning with fludarabine, cyclophosphamide, and alemtuzamab. The RA remitted completely. There was no GVHD or other significant complications [43]. At 5 years, she was in rheumatoid factor negative remission of the RA, but subsequently developed leukaemia in her sixties (personal communication, Dr Richard Burt).

### Conclusions

With the widespread use of biological therapies, and their relatively good safety profile, the use of SCT in RA is relatively rare now (Figure 2). A decade previously it had been the focus of intense investigations, which supported its role as a potential therapeutic modality in severe resistant patients for whom other treatment options are limited. It is extremely unlikely that a large randomised phase III study providing absolute proof of principle will ever report, but based on single arm observational data, the occasional application of this approach would be considered reasonable in carefully selected patients failing all other routine approaches, including licensed biological therapies. Such patients continue to be reported to the EBMT registry (Figure 2).

Overall, compared with other autoimmune diseases, patients with RA tolerate SCT well, with no reported treatment related mortality (compared with the relatively high rates in other autoimmune diseases with multiple internal organ involvement). Autologous SCT appears to be most effective in patients with seronegative RA. Based on the data, there should be an expectation of relapse, with the suggestion that early introduction of anti-rheumatic agents, or biological agents such as rituximab, may result in ongoing disease control. All cases should be reported to the EBMT registry or equivalent.

Data relating to syngeneic SCT is sparse, although, the possible cure of disease in one case may mean that it is a reasonable option, if the rare instance of a treatment resistant patient with a potential syngeneic donor arises. The curative potential of allogeneic SCT in RA continues to fascinate. However, only

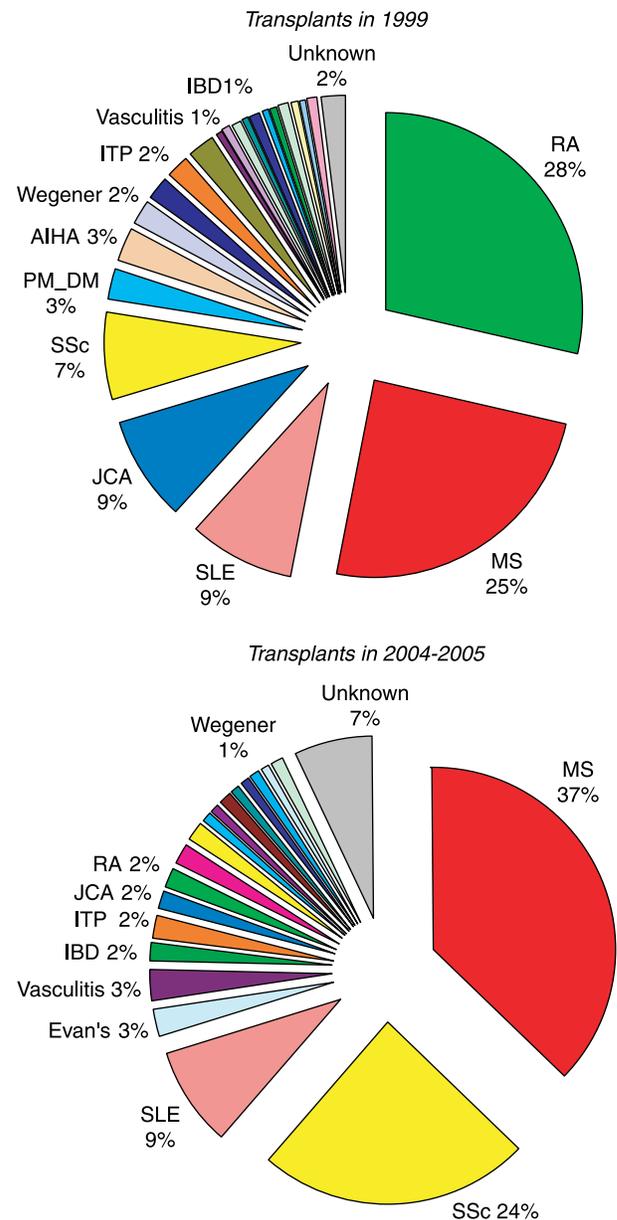


Figure 2. Relative frequency of SCT for RA in 1999 (the main indication) compared with 2004–2005 (only 2% of registrations; Source EBMT database, with permission).

one case has been documented to date and RA is rarely sufficiently severe to justify the associated levels of treatment related mortality and morbidity. Patients should only be treated in the clinical trial setting.

In summary, over a decade of clinical studies underpinned by animal models have provided a potential treatment modality in what are now rare patients with RA refractory to traditional and biological agents. In addition, the ablation of dysfunctional immune systems and their reconstruction with haemopoietic stem, and progenitor cells has provided further pathophysiological insights into this elusive disease process.

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