# Hematopoietic and mesenchymal stem cell transplantation in autoimmune diseases

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In the past decade, approximately 800 patients have received a hematopoietic stem cell transplant for the treatment of a severe autoimmune disease (AD). In all AD subgroups, long-term remissions (in approximately a third of cases), relapses, nonresponse and treatment-related mortality have been seen. Controlled randomized trials in systemic sclerosis, rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus are underway in Europe and the USA, as well as Phase II studies in Crohn's disease and chronic inflammatory demyelinating polyneuropathy. Laboratory studies suggest induction of long-term remission in some cases, despite the return of full, normal immune function. Recent data suggest the potential for stem cells, such as mesenchymal cells, to have an antiproliferative, immunomodulatory and tissue protective effect in AD, similar to that seen in acute graft-versus-host disease. A program to explore this further is underway and is described in this review.

A consensus statement was published in the *Lancet* 10 years ago outlining a structured approach for the use of hematopoietic stem cell transplantation (HSCT) in the treatment of severe, therapy-resistant autoimmune disease (AD) [1]. The events leading up to this consisted of coincidental observations of AD improving during HSCT given for conventional indications, animal model data supporting the concept [2,3] and a lack of alternative options for such patients. Underriding this concept was also the possibility, based on animal data and some single-case, long-term follow-up, that a state of tolerance may be induced after such immunoablative therapy followed by HSCT rescue.

Several international meetings took place on both sides of the Atlantic, from which emanated more detailed consensus statements [4,5], and the first case reports of HSCT performed for AD alone appeared soon afterwards [6,7].

Currently, there are approximately 800 patients who have received a HSCT for the treatment of a severe AD, 624 of whom are registered in the European Group for Blood and Marrow Transplantation (EBMT)/European League Against Rheumatism (EULAR) database. The analysis of the first 463 evaluable transplants registered before 2003 was published recently, showing that autologous HSCTs could alter the natural history of established AD with an overall transplant-related mortality (TRM) of 7% [8]. Most have been autologous HSCT, being less toxic than allogeneic HSCT due to the risk of graft-versus-host disease (GvHD). Despite initial theoretical argumentation that only allogeneic HSCT could replace a defective autoaggressive immune system, the autologous experience points more to a resetting of a dysfunctional immune system, rather than ablation.

This review summarizes the experience so far and indicates the future directions being planned, including the evolving concept of mesenchymal stem cell (MSC) immunomodulation.

## HSCT & coincidental autoimmune disease

Occasionally, patients receiving allogeneic and autologous HSCT for a conventional indication (e.g., aplastic anemia or malignancy) also coincidentally had an AD, with both conditions improving after transplantation. This largely positive experience, published as case reports and a small series over the past two decades, has been reviewed recently [9–11]. Initial reports were of allogeneic HSCTs and many of these patients remained free from both the primary target disease and the AD. In some patients, relapse of the original AD occurred, and in one such patient full engraftment with donor-type lymphocytes was observed [12]. More recent studies have reported durable responses following autologous HSCT [13], thus suggesting that genetic predisposition alone is not sufficient for AD expression [14].

Transfer of AD through allogeneic HSCT has also been described [15,16]. In one patient with leukemia, production of autoantibodies (anti-Clq) was detected following HSCT from a donor with known systemic lupus erythematosus (SLE); however, clinical disease did not develop [17].

## Treatment of human autoimmune disease with HSCT

Of the 800 patients receiving a HSCT as treatment of an AD alone, 624 (596 autologous) are registered in the EBMT and EULAR database (Table 1) and the remaining are registered in the International Bone Marrow Transplantation Registry (IBMTR) in the USA. In the EBMT/EULAR database, the majority of patients have had either severe multiple sclerosis (MS) or systemic sclerosis (SSc), and HSCTs were performed within the context of controlled Phase I/II studies.

In the EBMT/EULAR database the most commonly transplanted diseases are MS, SSc, rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and SLE, with data coming from over 100 transplant centers in more than 20 countries. There were long-lasting responses in all disease categories; however, these were achieved at a price, the overall actuarially adjusted TRM being 7% [8,18]. This was higher than the predicted 3% for autologous HSCT overall and reflects the general level of illness and multiorgan involvement of many AD patients compared with, for instance, breast cancer patients undergoing high-dose chemotherapy and HSCT. There is a marked difference between AD groups, with a TRM of 11% in SLE and only one patient (1.4%) with RA. There were also different rates and degrees of responses.

## Outcomes in Phase I/II trials

### Systemic sclerosis

Several protocols were used, mostly either Cy based (4 g/m$^2$ Cy mobilization and Cy 200 mg/kg body weight conditioning) or radiation (8 Gy/Cy 120 mg/kg body weight). An analysis of all Phase I/II pilot studies showed that in the first 65 patients, an improvement of 25% or more in the skin score (measured by the modified Rodnan method) was seen in 70% of the patients, with a TRM of 12.5% [19]. With further patient recruitment and longer term follow-up, the TRM of the EBMT-registered patients fell, possibly due to more careful patient selection. Lung function tended to stabilize in those patients with deterioration prior to transplant. Some factors were identified as potentially hazardous for HSCT, for example, pulmonary hypertension more than 50 mmHg mean pulmonary arterial pressure, severe cardiac involvement, severe pulmonary fibrosis and uncontrolled systemic hypertension. A long-term follow-up of this cohort showed an overall TRM of 8.7%, no further transplant-related deaths and durable remissions in more than a third of patients [13].

Based on the Phase I/II study experience, a prospective, randomized, comparative trial of HSCT (Cy, antithymocyte globulin [ATG] and CD34 selected graft) versus monthly intravenous pulse Cy 750 mg/m$^2$ for 12 months, the Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial [101] was initiated, which has so far randomized 62 patients (28 HSCT) with no treatment-related deaths in either arm.

A multicenter, US study of 19 SSc patients utilizing a regimen of Cy 120 mg/kg, total body irradiation (TBI) 8 Gy and equine ATG 90 mg/kg body weight and a CD34-selected graft product showed a sustained benefit in 12 patients at median follow-up of 14.7 months [20]. Four patients died, three from treatment-related causes and one from disease progression. In two cases, a fatal regimen-related pulmonary toxicity occurred, which was not seen in the subsequent 11 cases in whom lung shielding was employed. A total of 12 patients had a sustained and significant improvement of skin score and functional status to a degree not previously seen with other treatment modalities. A prospective, randomized study using similar selection criteria, control arm and end points as the ASTIS trial is planned in the USA under the auspices of the NIH. The treatment arm will, however, be different, being Cy and radiation based, allowing a comparison between the different regimens [K Sullivan, Pers. Comm.].

### Systemic lupus erythematosus

Of the 55 registrations in the EBMT/EULAR database, most had either renal and/or CNS involvement and 21 had failed conventional Cy treatment. A peripheral stem cell source after mobilization with Cy and granulocyte colony-stimulating factor (G-CSF) was used in the majority. A total of 23 patients received conditioning with Cy and ATG, 11 Cy plus TBI and four other regimens were employed. An unselected graft was used in 29 patients, with CD34 selection in 19. There were five deaths due to treatment and one from progressive disease, resulting in an actuarially adjusted TRM of 10% (range: 2–20).

In those 53 patients with sufficient data for analysis, 66% achieved remission, which is defined as a SLE disease activity index (SLEDAI) of less than or equal to 3 and steroid

## Table 1. EBMT/EULAR autoimmune disease autologous hematopoietic stem cell transplantation database, status in October 2004.

| Disease & disease category | Number of patients |
| --- | --- |
| *Neurological disorders* | |
| Multiple sclerosis | 183 |
| Myasthenia gravis | 2 |
| Polyneuropathy | 3 |
| Amyotrophic lateral sclerosis | 2 |
| Guillain–Barre syndrome | 1 |
| *Rheumatological disorders* | |
| Systemic sclerosis | 88 |
| Rheumatoid arthritis | 72 |
| Juvenile idiopathic arthritis | 54 |
| Systemic lupus erythematosus | 66 |
| Dermatomyositis | 7 |
| Mixed connective tissue disease | 4 |
| Behcet's disease | 5 |
| Psoriatic arthritis | 2 |
| Ankylosing spondylitis | 2 |
| Sjögren's syndrome | 1 |
| *Vasculitides* | |
| Wegener's | 4 |
| Cryoglobulinemia | 4 |
| Not classified | 2 |
| *Hematological immunocytopenias* | |
| Immune thrombopenia | 12 |
| Pure red cell aplasia | 4 |
| Autoimmune hemolytic anemia | 5 |
| Thrombotic thrombocytopenic anemia | 3 |
| Evan's syndrome | 2 |
| *Gastrointestinal disorders* | |
| Enteropathy | 2 |
| Inflammatory bowel disease | 3 |
| *Other* | 3 |
| *Total* | 536 |

*Courtesy of Dr R Saccardi, EBMT autoimmune disease working party.*

*EBMT: European Group for Blood and Marrow Transplantation; EULAR: European League Against Rheumatism.*

reduction to less than 10 mg/day. Of those achieving remission, 32% subsequently relapsed by some degree and most were easily controlled on standard agents that had been previously ineffective. There were 12 deaths after 1.5 months (range: 0–48), of which seven (12%) were related to the procedure in these severe SLE patients [21,22].

Traynor and colleagues reported a 5-year experience in 15 patients with severe SLE who were transplanted [23]. The group had previously reported one death as a result of infection following mobilization and another 3 months later from active CNS lupus, having not proceeded to transplant [24]. Of the 15 proceeding to transplant (mobilization with 2 g/kg and G-CSF

followed by conditioning with cyclophosphamide 200 mg/kg, methylprednisolone 1 g and equine ATG 90 mg/kg), all improved clinically and serologically with a median follow-up of 36 months (range: 12–66). This cohort has since been extended and reported with an improvement of pulmonary function tests [25], no further TRM and a positive clinical and laboratory response in patients experiencing the antiphospholipid syndrome [26].

### Rheumatoid arthritis

A retrospective analysis of the first 78 registered patients showed significant improvement, with 67% achieving an American College of Rheumatology (ACR)50 response at

some time post transplant [27]. Most of the patients had failed a median of five (range: 2–9) conventional disease-modifying antirheumatic drugs (DMARDs) before the transplant. Some degree of relapse was seen in 73% of patients post transplant, but in most cases was relatively easy to control with drugs that had proven ineffective prior to transplant. At 12 months post transplant, more than half of the patients had achieved an ACR50 or more, and of these, just over 50% had not restarted DMARDs. The median follow-up was 18 months (range: 6–40) and at this time the majority of patients had received a conditioning regimen of Cy 200 mg/m$^2$ alone followed by peripheral blood stem cells mobilized with G-CSF or Cy/G-CSF (equal numbers). Only one TRM was reported, a patient who, 5 months post transplant (busulphan/Cy), died from sepsis, with a coincidental non-small cell lung carcinoma being discovered at autopsy. In the opinion of the investigators, this was not considered to be a transplant-induced tumor.

A multicenter trial in Australia failed to show any advantage of CD34$^+$ selection of the graft after nonmyeloablative conditioning with Cy [28].

### Phase I/II juvenile idiopathic arthritis

A total of 54 children with JIA, mostly the systemic form called Still's disease, were registered. Most of these cases were treated in two Dutch centers using stem cells obtained from bone marrow and a conditioning protocol of Cy 200 mg/kg body weight, TBI 4 Gy and ATG [29]. In the follow-up report of 34 patients there were 18 complete drug-free remissions and six partial remissions [30]. In those attaining remission, the corticosteroid dose could be reduced and some patients experienced puberty and catch-up growth. Three patients died from hemophagocytic syndrome, also called the macrophage activation syndrome, thought to be related to intercurrent infection or uncontrolled systemic activity of the disease at the time of transplantation. Protocols were modified accordingly, such that systemic activity is controlled before the transplant with intravenous methylprednisolone. Since this modification, 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 [N Wulffraat, Pers. Comm.]. Further Phase II studies will be performed to assess the optimal regimen for a Phase III study.

### Crohn's disease

Autologous HSCT has been performed in approximately 16 patients for the treatment of refractory Crohn's disease. The largest series, from Chicago, IL, USA, showed a sustained clinical improvement in 11 out of 12 patients with a median follow-up of 18.5 months (range: 7–37) [31]. Protocols have generally followed published guidelines [32] and a multicenter trial is soon to be launched in Europe under the auspices of the EBMT and the European Crohns Colitis Organisation [C Hawkey, Pers. Comm].

### Allogeneic HSCT

A graft-versus-autoimmunity effect has been postulated as a result of the graft-versus-host reaction. This was first observed in a patient undergoing an allogeneic HSCT for chronic myeloid leukaemia, whose severe psoriasis also improved [33]. This is also compatible with long-term control in RA in a small number of allografted patients. These patients had received conditioning regimens similar to those given in trials of autografting in RA (i.e., Cy 200 mg/kg), and the longer remission in the allografted patients suggest that the type of graft, rather than the conditioning regimen, determined the outcome. However, both long-term remissions with autologous HSCT and relapses following allogeneic HSCT (with full donor chimerism) have been observed in AD post transplant, as well as newly occurring AD [34–37].

Newer techniques with nonmyeloablative conditioning regimens may reduce early TRM to less than 10%, making allogeneic HSCT for AD more acceptable. The theoretical concept of tolerance induction in the thymus due to stable mixed chimerism has been elegantly reviewed recently [38]. There have been several early reports, one with an SLE/scleroderma overlap syndrome [39] and one with RA [40]. However, the risk of GvHD remains, and it is unclear whether the target cells for HSCT in AD can be defined as clearly as in malignant and inherited disorders.

### Immune reconstitution

In a recent pivotal study, Moraro and colleagues showed that in a group of MS patients, clinical improvement was sustained even after full immune reconstitution, as assessed by the normal distribution of the T-cell receptor Vβ gene usage.

The finding of T-cell receptor excision circles (TRECS) in T cells recently exiting the thymus [41] has allowed a more detailed analysis of

normal and autoaggressive T-cell reactions following HSCT for AD. Following HSCT for AD, some adult patients have shown an increase in the number of lymphocytes bearing TRECS, indicating that the thymus may become reactivated and theoretically capable of inducing central tolerance.

## MSCs in autoimmune disease

The causative mechanism for most ADs is unknown but involves a complex interplay between genetic and environmental factors [14] and is executed through interdependent cascades of immunological, inflammatory and fibrotic pathways [42]. An alternative therapeutic strategy might derive from the exploitation of the immunomodulatory properties of MSCs.

MSCs are currently the subject of intense study with respect to their ability to regenerate tissue [43], support hemopoiesis [44] and act as stable vehicles for a variety of vectors used in gene transfer [45]. Much interest has recently been generated by the observation that they may also exert a profound immunosuppressive and anti-inflammatory effect both *in vitro* and *in vivo* [46–50].

As yet, no single specific MSC immunophenotyping marker has been identified, since many antigens expressed by MSCs are also present on many other cell types. Therefore, the identification of MSCs is based on a combination of evidence of their differentiation properties into multiple mesenchymal lineages [51] and the expression of several molecules, including differentiation and lineage specific markers, adhesion molecules, extracellular matrix and growth factor receptors.

A generally accepted panel of positive markers includes CD29, CD73, CD90, CD105 and CD166, as well as being negative for the hematopoietic markers CD14, CD34 and CD45 **(Table 2)** [51–55].

A true stem cell status is not established (i.e., capable at a single cell level *in vivo* of regeneration or maintenance of a tissue compartment), nor have they been shown to be able to have both constant self-renewal and give rise to one or more differentiated progeny [56–58].

For this reason, they are called multipotent mesenchymal stromal cells [59] or simply mesenchymal progenitor cells (MPCs) by some authors [60]. *In vitro*, they have a vast proliferative potential, clonally regenerate and give rise to differentiated progeny [51].

The origin of MSCs is unclear, but could be from a wave of similar cells found in the blood during the 7th and 12th week of gestation that populate the bone marrow and other stromal compartments. MSCs are found in fetal liver and bone marrow just prior to the onset of definitive hematopoiesis at those sites [61]. Recent work has shown that MSCs are present in fetal bone marrow from as early as 9 weeks gestation before hemopoiesis becomes established. Prior to that, they circulate in fetal blood in fairly high numbers from at least 7 weeks' gestation. Fetal MSCs are phenotypically similar to adult MSCs but have greater multipotency (including myogenic, endothelial and neural potential), which is maintained through more divisions, gives rise to more frequent colony-forming unit fibroblasts (CFU-Fs) and has more robust and rapid growth profiles [62].

The most well-studied and accessible source of MSCs is bone marrow, although even in this tissue the cells are present in a low frequency (0.01–0.0001% of the nucleated cells). As well as being present in bone marrow, MSCs have also been isolated from peripheral blood, fat and synovial tissue [63]. They may be expanded up to a billion fold and, if plated at low density, they do not lose their multilineage differentiation potential [51].

## Immunomodulatory properties of MSCs
### In vitro

The initial studies addressing the immunological properties of MSCs showed that not only do they fail to stimulate allogeneic T cells, but they also exhibit an active immunosuppressive effect. Such an effect is dose dependent and is exerted on T-cell responses to both polyclonal stimuli such as those induced by mitogens or by polyepitope mixed lymphocyte reactions [47,64,65], and to their cognate peptide [66]. The inhibition does not appear to be antigen specific [64] and targets both primary and secondary T-cell responses [66]. However, it may still exert some selectivity as it appears to discriminate between cellular responses to alloantigens and recall antigens [67].

The lack of antigen specificity is also supported by the evidence that T-cell suppression is not cognate antigen dependent, as it can be observed using HLA class I-negative MSCs and can be exerted by MSCs of different major histocompatibility complex (MHC) origin from the target T cells [65]. The inhibitory effect of MSCs is directed mainly at the level of cell proliferation as a result of cyclin D2 downregulation and p27 upregulation [48]. Therefore,

## Table 2. Phenotype of multipotent mesenchymal stromal cells.

| CD no. | Other name(s) | Location/function | Positive/negative |
|---|---|---|---|
| CD29 | None | Leukocytes<br>Integrin-β1 subunit | Positive |
| CD73 | SH-3, -4 (epitopes)<br>Ecto-5′-nucleotidase | T- and B-cell subsets | Positive |
| CD90 | Thy-1 | CD34+ prothymocytes<br>Function: unknown | Positive |
| CD105 | SH-2<br>Endoglin | Endothelial cells<br>Activated mono/macro<br>Bone marrow cell subsets<br>Function: binds TGF-β | Positive |
| CD166 | ALCAM | Activated T cells<br>Thymic epithelium<br>Fibroblasts/neurons<br>Function: ligand for CD6 | Positive |
| CD14 | Myelomonocytes | LPS receptor | Negative |
| CD34 | None | Hematopoietic precursors<br>Capilliary endothelium<br>Function: unknown | Negative |
| CD45 | Leukocyte common antigen | All hematopoietic cells<br>Function: augments T- or B-cell<br>receptor signaling | Negative |

*ALCAM: Activated leukocyte cell adhesion molecule; LPS: Lipopolysaccharide; SH: Src homology; TGF: Transforming growth factor.*

MSC-mediated inhibition induces an unresponsive T-cell profile that is fully consistent with that observed in division arrest anergy [68]. Such a state appears to be irreversible [48], as also suggested by the evidence that T cells undergo apoptotic changes. However, *in vivo* data appear to contradict these *in vitro* results [49].

The mechanisms underlying the immunosuppressive effect remain to be clarified. Although the use of different methods and/or different species to generate MSCs have produced conflicting results, overall data suggest that both soluble factors [47,69–71] and cell contact-mediated mechanisms are involved [66,67,69–72]. As far as soluble factors are concerned, a few potential candidates have been suggested. Indoleamine 2,3-dioxygenase (IDO), an enzyme that, by catalyzing the conversion from tryptophan to kynurenine, exerts a major immunosuppressive effect on T-cell responses, has been shown to be produced by MSCs stimulated by proinflammatory cytokines [71]. Similarly, MSCs produce hepatocyte growth factor (HGF), transforming growth factor (TGF)-β [47] or prostaglandins [73], which appear to contribute to their lymphocyte proliferation inhibitory effect.

Some studies have suggested that MSC-mediated immunosuppression could rely on other mechanisms involving the contribution of cells with specific immunomodulatory activity. Although CD4+/CD25+ regulatory T cells are not required for MSC-mediated inhibition to be achieved [66], some have demonstrated the participation of CD8+ suppressor T cells in the effect [70]. Interestingly, interleukin (IL)-10 and TGF-β, both produced by MSCs, can induce CD4+CD25- cells to acquire regulatory properties. IL-10 secretion by MSCs has also been implicated in playing a major role in the immunosuppressive effect by determining a T-helper cell (Th)1–Th2 shift [72]. There is now ample eidence that MSCs also prevent the *in vitro* generation of mature dendritic cells from monocytes and the subsequent failure of these cells to stimulate T-cell responses. This generalized effect suggests that MSCs possess nonspecific immunosupressive actions, as demonstrated by the observation that B cells are also susceptible to the MSC effect **(Figure 1)** [48,74]. Despite the probable multiple mechanisms, MSCs have great potential to become a new tool in the list of cellular therapies for ADs.

*In vivo*

The initial observation that *in vivo* administration of MSCs in baboons significantly prolongs the survival of MHC-mismatched skin grafts [64] has been tested in the clinical setting, whereby a patient with severe acute GvHD following an allogeneic bone marrow transplant was successfully treated with the infusion of a third-party MSC from a haplo-identical donor [75]. However, there was some return of minimal residual tumor in this case, as has also been suggested in a murine melanoma metastasis model [70].

In animal models of AD, results are inconsistent. In a murine MS model, amelioration of the clinical and histological state was demonstrated by two groups, thought to be due to anergy in one [49] and production of anti-inflammatory and neuroprotective factors in

another [76]. Djouad and colleagues showed a worsening of a murine collagen-induced arthritis model, considered to be due to a TNF-$\alpha$ negation of the immunosuppressive effects of MSCs [44].

In summary, MSCs are immune privileged and impart antiproliferative, immunomodulatory and anti-inflammatory tissue-protective effects following homing to damaged tissues. Their features strongly support their exploitation in ADs if further substantiated in animal models. Although early data in humans suggest that their toxicity is negligible, most such patients have been heavily immunosuppressed in the context of GvHD. Long-term follow-up safety data are required on all humans receiving MSCs therapeutically, given the possibility of transformation in culture to malignant tumors [77]. This would need to be weighed against the established risk of malignancy in long-term immunosuppressed patients with refractory AD.

## Future perspective

Immunoablation with HSCT has been applied to over 800 severe AD patients in Phase I/II studies and found to result in durable, drug-free remissions in over a third of cases. The final setting of such a tolerance-inducing therapy is now being established through international, randomized, prospective, controlled trials in SSc, MS, Crohn's disease and SLE. The stem cells are assumed to be exerting a purely supportive role, shortening the period of aplasia.

Recent work suggesting that another bone marrow-derived stem cell, the MSC, may exert both an immunosuppressive and tissue-protective effect has led to the application of marrow-derived and *ex vivo*-expanded allogeneic MSCs in severe acute GvHD, with early success. It is possible that MSCs may also be of use in severe, inflammatory AD with potentially anti-inflammatory, antiproliferative and immunosuppressive properties. Although immune privileged across allogeneic barriers, it would be ideal if autologous MSCs were equally effective. Some animal models and early human *in vitro* work suggest this, and intense interdisciplinary collaboration is underway to establish proof-of-principle. Study protocols should be developed together within the context of established societies, such as the EBMT and International Society for Cellular Therapy, with already extensive experience in cellular therapies, good manufacturing practices, expansion protocols and long-term safety follow-up data collection.



**Figure 1. Inhibition of T- and B-cell proliferative responses.**
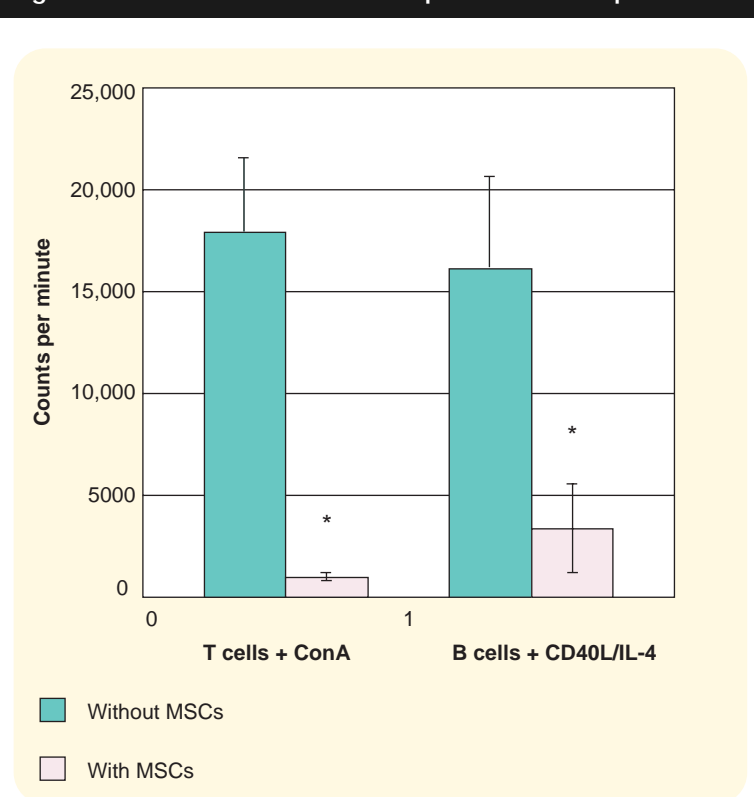
B-cell splenocytes ($1 \times 10^5$), obtained by removing T cells using mouse anti-Thy1.2 Dynal beads, were stimulated with anti-CD40 monoclonal antibodies ($2\ \mu g/ml$) and IL-4 ($10\ \mu g/ml$) in the presence or absence of MSCs ($1 \times 10^4$). As a comparison, unfractionated C57BL/6 splenocytes ($1 \times 10^5$) were stimulated with $10\ \mu g/ml$ ConA. $^3$H-Tdr was added to cultures on day 2, and cell proliferation assessed on day 3. Results are the average of three experiments of identical design; bars show the standard deviation.
*Statistically significant ($p < 0.01$).
ConA: Concanavalin A; IL: Interleukin; MSC: Mesenchymal stem cell; Tdr: Thymidine deoxyribose.

## Executive summary

### Background & Phase I/II results of hematopoietic stem cell transplant trials

- Animal models and coincidental cases 10 years ago led to the application of hematopoietic stem cell transplant (HSCT) to autoimmune disease (AD) (approximately 800 patients have now been treated).
- The most common ADs treated are multiple sclerosis (MS), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvanile idiopathic arthritis and idiopathic thrombocytopenic purpura.
- Most protocols have been autologous (less toxicity due to graft-versus-host disease [GvHD]).
- Approximately a third of patients have responded with durable, drug-free remissions.
- Overall transplant-related mortality (TRM) was 7% – with very little in the past 3 years. General toxicity remains as seen previously with HSCT.
- The more intense regimens (radiation based or full myeloablative) did not impart an equivalent advantage concerning response and relapse rates.

### Randomized studies

- In Europe, prospective randomized trials are running in SSc (Autologous Stem cell Transplantation International Scleroderma trial), MS (Autologous Stem cell Transplantation International Multiple Sclerosis trial) and RA (Autologous Stem cell Transplantation International Rheumatoid Arthritis trial). Currently, there has been no TRM in either arm of any study.
- In the USA, randomized trials in SSc and SLE are planned/running. Phase II trials in MS are also planned.

### Immune reconstitution

- In general, immune reconstitution has reflected previous experience with delayed naïve T-cell reconstitution, for up to several years in some cases.
- Failure of disease relapse, despite fully normal immune reconstitution, indicates potential resetting of the autoimmune process.

### Mesenchymal stem cells

- Mesenchymal stem cells (MSCs) are obtained from bone marrow and have a vast expansion capacity *ex vivo* without losing their stem properties.
- They are immune privileged across allogeneic barriers and able to impart antiproliferative, anti-inflammatory and immunomodulatory effects.
- MSCs are characterized by surface markers, such as CD29, CD73, CD90, CD105 and CD166, some of which are adhesion and integrin molecules, allowing them to home to distressed tissues.
- Animal models of tissue stress, AD and human acute GvHD are ameliorated by MSCs in a cell and noncell contact fashion.
- A paracrine effect involving molecules such as transforming growth factor-β and interleukin-10, rather than tissue differentiation, are the most likely effector mechanisms leading to a state of anergy.
- Although acute toxicity seems low, long-term follow-up is important concerning the loss of tumor immunity.

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Website

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