Stem cell therapy: resetting autoimmunity or postponing the inevitable?

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Autoimmune diseases (ADs) comprise a heterogeneous group of conditions characterized by the presence of autoantibodies and/or T- or B-lymphocyte reactivity against autoantigens. In many conditions the precise relationship between autoimmune responses and clinical features remains to be defined, but the prevailing notion is that failure of central or peripheral immune tolerance leading to autoimmunity precedes clinically overt autoimmune disease which in the case of rheumatic autoimmune conditions is characterized by systemic inflammation, vasculopathy and signs and symptoms of musculoskeletal involvement. Except for rheumatoid arthritis (RA), rheumatic autoimmune diseases are rare, affecting less than 1% of the population. Nevertheless, they account for a high share of public health expenditure, due to their chronic debilitating nature [Gabriel and Michaud, 2009]. It is not therefore surprising that new therapeutic avenues are constantly being explored. While biologicals have resulted in major breakthroughs in the treatment of RA and juvenile idiopathic arthritis (JIA), connective tissue diseases such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) still pose major challenges to clinicians seeking effective treatment options. Biologicals which interfere with the immune response such as rituximab (anti-CD20 mAb) and abatacept (CTLA4-Ig) have not been proven more effective than placebo in controlled clinical trials, which contrasts with the positive collective rituximab experience from large case series. Belimumab (anti-BAFF mAb) is the first new drug to be licensed for use in SLE for several decades, but its efficacy is modest, and its place in the treatment paradigm of lupus remains to be established. Imatinib was hailed as a promising drug for the treatment of systemic sclerosis based on its mechanism of action and on studies in animal models of scleroderma, but it is unlikely that its

clinical development in systemic sclerosis will be pursued following disappointing results from pilot studies. Conventional immunosuppressive drugs including glucocorticoids, cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil therefore still remain the cornerstone in the treatment of connective tissue diseases. However, long-term drug-free remissions are rare and adverse drug reactions and clinical sequelae of long-term use contribute to compliance problems.

The search for effective therapies continues unabated and it is in this context that haematopoietic stem cell transplantation (HSCT) has been used as a means of controlling otherwise resistant disease activity, or even inducing drug-free remission in severe AD. HSCT is a complex therapeutic intervention, comprising mobilization of haematopoietic progenitor cells using high-dose chemotherapy and granulocyte colony-stimulating factor (G-CSF) or harvest of bone marrow, followed by intensification with myeloablative or lymphoablative doses of chemotherapy and/or lymphocyte-depleting antibodies and/or total body irradiation, and (re)infusion of the graft to reduce the duration of aplasia. The first studies of the curative potential of HSCT in animal models of SLE were conducted several decades ago [van Bakkum, 2004; Morton and Siegel, 1979]. Clinical observations of long-term remissions in ADs patients who were treated with allogeneic HSCT for haematological indications supported the concept of immunoablation [Marmont, 2004]. From 1995 the first procedures were initiated specifically for ADs, and from 1996 onwards data were centrally collected in a registry of the EBMT Autoimmune Disease Working Party (ADWP), in collaboration with organizations such as EULAR. Core data from over 1000

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patients with severe, refractory AD who underwent autologous HSCT have now been collected and analysed.

Among 900 patients undergoing autologous HSCT (which included 175 patients with SSc, 85 with SLE, 89 with RA, 65 with JIA) the overall 5-year survival was 85%, and progression-free survival (PFS) 43%, but with great variation between ADs, with age <35 years, HSCT after 2000, diagnosis and a centre activity effect associated with outcome [Farge *et al.* 2008]. RA patients tolerated HSCT best as illustrated by a low transplant-related mortality (TRM) (1%), when compared with SLE, JIA, and SSc patients where TRM ranged from 7% to 12%. In contrast, PFS was better in SSc and SLE patients, due to high relapse rates in RA and JIA patients. While many lessons have been learned from registry analyses, these results should be interpreted with caution, however, as different treatment regimens were used for different conditions. For example, RA patients were generally treated with the least intensive conditioning regimen (high-dose cyclophosphamide), and studies on synovial tissue taken pre- and post-HSCT have shown persistence of mononuclear cell infiltrates [Verburg *et al.* 2005; Bingham *et al.* 2002; Brinkman *et al.* 2002]. It is conceivable that these contained residual autoimmune effector cells whose homeostatic proliferation in a lymphopenic environment contributed to relapse. Such issues do not play a role in allografting. Allogeneic HSCT has theoretical advantages over autologous HSCT. First, allografting is based on the use of stem cells from a major histocompatibility complex (MHC)-matched healthy donor, which should have a normal differentiation potential. Second, allografting has the potential benefit of inducing a graft-*versus*-autoimmunity effect, albeit at the risk of graft-*versus*-host disease. The latter can manifest itself as a scleroderma-like

disease associated with significant morbidity. A limited number of patients with AD have undergone allogeneic HSCT. A retrospective analysis of these cases confirmed the ability to achieve prolonged responses in some patients, but with significantly more toxicity than in autologous HSCT with a TRM of 25% [Daikeler *et al.* 2009]. While the risks and toxicities of allografting may be justified in lethal diseases such as acute leukaemias, the general consensus is that allografting is not the first HSCT option in AD patients.

In contrast to immunosuppressive medication and biologicals, HSCT does not merely suppress the immune system functionally or numerically, but has the potential to induce fundamental alterations of the immune system which are prerequisites for attaining longlasting remission. Ideally these effects include: (1) creation of space so that reinfused haematopoietic stem cells can home and form new niches for differentiation; (2) depletion of autoaggressive T and B lymphocytes; (3) abrogation of inflammation; (4) restoration of immune regulation; (5) reversal of stromal cell abnormalities. The impact of HSCT on immune function was originally referred to as ‘resetting the immunostat’ in analogy to rebooting of a computer. Translational studies in transplanted patients lent support to the concept (Table 1), but whether the published immune effects were the cause or a consequence of a state of remission is unknown and probably difficult to determine anyway. As yet there is no biomarker of immune tolerance which can be reliably used in clinical studies to predict the effects of HSCT. As outlined above, remission has not been achieved in all transplanted patients, and relapses have been particularly common in RA and JIA [Brinkman *et al.* 2007; Verburg *et al.* 2001]. Relapses could be due to insufficient eradication of autoaggressive lymphocytes, to intrinsic defects of stem cells,

Table 1. Mechanistic effects of haematopoietic stem cell transplantation in rheumatic autoimmune disease.

1. Induction of regulatory T cells (JIA, SLE)	[Petri <i>et al.</i> 2010; Alexander <i>et al.</i> 2009; Roord <i>et al.</i> 2008; de Kleer <i>et al.</i> 2006]
2. Restoration of cytokine imbalances (JIA)	[Roord <i>et al.</i> 2008]
3. Reduction of autoantibodies (RA, SLE)	[Alexander <i>et al.</i> 2009; Teng <i>et al.</i> 2007]
4. Resolution of fibrosis (SSc)	[Verrecchia <i>et al.</i> 2007]
5. Induction of angiogenesis (SSc)	[Aschwanden <i>et al.</i> 2008; Fleming <i>et al.</i> 2008]

JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis.

renewed formation of autoaggressive lymphocytes, or contamination of the graft with autoaggressive lymphocytes. In the absence of marker studies it is difficult to distinguish between the different possibilities, but a study on T-cell receptor usage in transplanted multiple sclerosis suggests that the contribution to relapses of T cells in the graft is probably limited.

Based on the encouraging results from registry analyses and pilot studies, prospective, controlled, randomized-clinical trials were launched in SSc: the ASTIS-trial in Europe and the SCOT-trial in North America. Both aim to compare safety and efficacy of HSCT *versus* intravenous pulse cyclophosphamide, considered the standard treatment for severe forms of SSc. The ASTIS and SCOT trials use similar eligibility criteria and comparable outcome measures and include control treatment with 12 monthly intravenous pulses cyclophosphamide, but differ in conditioning without (ASTIS) or with (SCOT) irradiation, allowing future comparison. Accrual in the ASTIS trial is completed with 156 patients randomized; the SCOT trial is still accruing. The first results of the ASTIS trial will become available in 2011. The primary endpoint is event-free survival, and it is hoped that the short-term risks of HSCT are outweighed by better long-term survival. Long-term follow up of patients in these trials is essential to examine possible divergence of survival and study late effects. Future studies should address the importance of CD34+ selection of the graft and/or *in vivo* T-cell depletion if HSCT proves to be superior in terms of risk/benefit to conventional intravenous pulse cyclophosphamide.

In the past decade HSCT has evolved from an experimental treatment option to a viable therapy especially for patients with poor-prognosis connective tissue disease, as reflected by the forthcoming publication of new guidelines on the use of HSCT in AD. It is anticipated that the results of the ASTIS trial and SCOT trial may have wide implications if HSCT proves superior to continued immunosuppressive therapy. Nevertheless, many questions remain. First, not all patients with clinical features of AD have demonstrable autoimmunity, so how does HSCT work in these cases? *Vice versa*, long-term remissions have been reported in transplanted patients with persistent positive autoantibody status, an

indication that full correction of autoimmunity is not a precondition for HSCT to exert its effects. Second, several case reports have suggested HSCT improves signs of vasculopathy. Does this imply that HSCT contributes directly to tissue repair? Interestingly, *ex vivo* studies have shown that the CD34+ population contains progenitors of angiogenesis [Rookmaaker *et al.* 2005]. Third, HSCT is an expensive treatment, and is associated with considerable toxicity in some patients, and it would therefore be important if responsiveness to HSCT can be predicted. At the moment no individual clinical feature or laboratory marker or combination of markers has any clinical utility in predicting responsiveness to HSCT, but it is conceivable that better profiling will help clinicians to better select patients in the future. Last but not least, what component of HSCT confers its clinical and immune effects? It is commonly believed that conditioning with high-dose chemotherapy (with or without lymphoablative antibodies or TBI) is the critical step in inducing sustained responses, but *in vitro* data suggest that CD34+ cells themselves can also have immunomodulatory effects [Allakhverdi *et al.* 2009]. Furthermore, high-dose cyclophosphamide alone was not superior to monthly intravenous cyclophosphamide in a small randomized trial in patients with severe SLE [Petri *et al.* 2010]. Once the mechanism of action is understood, optimization of transplant protocols may lead to a treatment that combines the efficacy of current transplant protocols with improved safety.

HSCT continues to have appeal as a salvage therapy for patients with severe AD, notably those with poor-prognosis SSc and SLE. Effective treatment options are nowadays available for RA and JIA patients which are safer than HSCT. Whether HSCT is effective in RA and JIA patients refractory to biological remains to be demonstrated. Given the risks and costs of HSCT, many healthcare insurers will only reimburse treatment costs if HSCT is done in the context of a registered clinical trial. From a scientific perspective a prospective, randomized trial remains the gold standard. HSCT is not a cure for all, however, and in the absence of predictors of responsiveness (or toxicity for that matter), any transplant procedure in a patient with autoimmune disease remains a challenging venture with unknown long-term outcome.

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Conflict of interest statement

None declared.

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