

Review

Adult stem cells in the treatment of autoimmune diseases

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During the past 10 yrs, over 700 patients suffering from severe autoimmune disease (AD) have received an autologous haematopoietic stem cell transplant as treatment of their disorder with durable remission being obtained in around one-third. The most commonly transplanted ADs have been systemic sclerosis (scleroderma), multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis and systemic lupus erythematosus. A fewer number of patients have received an allogeneic transplant. The initially reported overall treatment-related mortality of 7% has since fallen, with no further cases being reported in systemic sclerosis or multiple sclerosis in the past 3 yrs. This is thought to be due to more careful patient selection. The phase I/II data has led to currently running prospective randomised trials in systemic sclerosis, multiple sclerosis and systemic lupus erythematosus in Europe and North America. Immune reconstitution data suggests a 'resetting' of autoimmunity in those patients achieving stable remission, rather than simply prolonged immunosuppression. Recent results from *in vitro* experiments, animal models and early human experience in severe acute graft vs host disease suggest that multipotent mesenchymal stromal cells obtained from the bone marrow and expanded *ex vivo*, may exert a clinically useful immunomodulatory effect. Such cells are immune privileged and apparently of low toxicity. Further characterization of these cells and consideration of their possible clinical application in AD is underway.

KEY WORDS: Stem cell, Transplantation, MSC, Autoimmune disease, Scleroderma.

Introduction

This year (2006) marks the 10th anniversary of the international stem cell transplant project in autoimmune disease (AD). Since 1996, data from over 700 cases of AD have been collected by the European Group for Blood and Marrow Transplantation (EBMT)/European League Against Rheumatism (EULAR) Autoimmune Disease Working Party in close collaboration with networks in the US where a further several hundred AD patients have been transplanted. Many patients have experienced long-term disease remissions, and immune reconstitution studies have shed light on pathophysiological mechanisms. In addition, resulting from the close association with transplantation medicine, the past several years have seen a growing interest in the role and potential therapeutic application of mesenchymal stem cells (MSCs) in AD. This collective experience and future directions are the subject of this review.

Rationale

Haematopoietic stem cell transplantation (HSCT) is the short name for a complex, multistep treatment, aimed at resetting the dysregulated immune system of patients suffering from severe AD. Its rationale is based on studies in experimental animal models of AD [1], including autologous tolerance induction and observations of remissions of AD in patients treated with HSCT for haematological malignancies [2], in some cases for nearly two decades [3]. Various protocols have been employed depending on the underlying disease and individual experience of transplant

centres, but most were based on autologous HSCT and involved the following consecutive interventions: (1) mobilization of peripheral blood progenitor cells using bolus infusions of cyclophosphamide plus s.c. injections with granulocyte colony stimulating factor (G-CSF), (2) high dose chemotherapy with or without lymphodepleting antibodies or total body irradiation (TBI) (referred to as 'conditioning') and (3) reinfusion of the graft product with or without manipulation *ex vivo*.

Although the principle therapeutic component of HSCT is the immunoablation (step 2), there is evidence that steps 1 and 3 may modulate the safety and effectiveness of the procedure and as such stem cell transplantation may be more than just a means to dose-escalate immunosuppressive medication. A key difference with the so-called 'targeted therapies' is that HSCT non-specifically affects a wide array of immune competent cells, which include B- and T-lymphocytes, thus creating space for a new immunological repertoire, generated from haematopoietic stem cells [4]. Depending on the components of the immunoablative regimen, stem cells may or may not be targeted as well. Most regimens employed in AD contained high doses of cyclophosphamide with or without anti-thymocyte globulin (ATG), which is non-myeloablative because stem cells are resistant to cyclophosphamide.

HSCT in rheumatic autoimmune disease

While HSCT quickly became an established treatment for many haemato-oncological conditions since it was first used to treat leukaemia over 30 yrs ago, its application in AD has long been

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hampered by concerns that HSCT might not be feasible or was too toxic in immunosuppressed patients with poor functional status and organ involvement from the underlying rheumatic disease.

The learning curve has indeed been steep, but the feasibility of HSCT in human AD has now been firmly established. With respect to safety and efficacy, some trends have emerged from retrospective database analyses and prospective pilot studies, even taking into account the limitations inherent in such studies [5]. More intense regimens were associated with higher treatment-related mortality but only a slightly lower probability of relapse, although differences in regimens, patient entry criteria and outcome parameters preclude more refined analyses. Importantly, the safety of HSCT has improved as best illustrated by the dramatic decrease of transplant-related mortality (TRM) in patients with severe systemic sclerosis (SSc). The TRM dropped from 17% in the first cohort of 41 patients entered in the EBMT/EULAR database [6] to 8.7% in a more recent analysis of 65 patients (which included the 41 mentioned) [7], and none in the 28 patients randomized to the transplant arm of the Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial [8] succumbed so far (discussed subsequently). A similar trend has been observed in multiple sclerosis (MS), the disease that accounts for most of the cases in the EBMT/EULAR database (Table 1). Also, with few exceptions, unexpected toxicities such as lymphoma and opportunistic infections have not been reported beyond that which is known for HSCT in general. This is not to say that toxicity has not been an issue. Major adverse events have been documented, most notably in SSc, systemic lupus erythematosus (SLE) [9] and juvenile idiopathic arthritis (JIA) [10].

TABLE 1. ProMISe database EBMT/EULAR Autoimmune Disease Working Party Most autologous (37 allogeneic). Registry update November 2005

Disease	No
Rheumatological disorders	
Systemic sclerosis	120
Rheumatoid arthritis	85
Juvenile idiopathic arthritis	64
Systemic lupus erythematosus	77
Dermatomyositis/polymyositis	7
Mixed connective tissue disease	4
Behcet's disease	8
Psoriatic arthritis	2
Ankylosing spondylitis	2
Sjogren's syndrome	1
Other	5
Vasculitides	
Wegener's	6
Cryoglobulinaemia	8
Other	17
Neurological disorders	
Multiple sclerosis	204
Other	8
Haematological immunocytopenias	
Immune thrombopenia	16
Pure red cell aplasia	7
Autoimmune haemolytic anaemia	11
Evans syndrome (immune thrombocytopenia and haemolytic anaemia)	9
Other	11
Gastrointestinal	
Inflammatory bowel disease	5
Other	3
Other/unknown	22
Total	702

EBMT Autoimmune Disease Working Party, courtesy of Dr R. Saccardi.

These included respiratory insufficiency during conditioning (SSc) [11] graft failure (SLE) [12], and macrophage activation syndrome (JIA) [13], which accounted for the majority of TRM in these diseases. Most transplant teams have since managed to circumvent these problems by adjusting protocols (e.g. by less intense T-cell depletion in JIA; lung shielding with TBI in SSc) and excluding patients with advanced disease and irreversible organ dysfunction.

While establishing feasibility, and safety was the priority in the early phases of the project, attention then turned to efficacy, since impressive clinical responses had been observed in many individual cases. There has been a striking difference between the disease targeted, responsiveness and toxicity (Fig. 1), although differences in protocols may have acted as a potential confounder. Marked improvements of disease activity, functional ability and quality of life were seen in the majority of JIA patients, resulting in restoration of growth after corticosteroid therapy was discontinued [10]. Many children were able to stop immunosuppression for over 5 yrs post-HSCT. Nevertheless, late relapses have occurred. In SSc, durable skin softening in patients with established generalized skin thickening has been observed in the majority of patients transplanted, defying conventional wisdom that fibrotic skin abnormalities are irreversible [7]. Such results are reminiscent of similar observations in patients with systemic amyloidosis treated with HSCT [14]. In SLE patients, disease activity as measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score improved dramatically [9], and in those with pulmonary abnormalities, lung function tests showed significant improvements in the years following HSCT [15, 16]. In contrast, most rheumatoid arthritis (RA) patients showed only transient responses, as measured by scores of disease activity, functional ability, quality of life and rate of joint destruction, although the disease appeared more amenable to anti-rheumatic medication post-HSCT [17, 18]. Two cases of syngeneic HSCT have been reported, one with a long-lasting remission [19], the other with a rapid relapse [20], while allogeneic SCT in another patient also resulted in a remission of RA [21]. Allogeneic HSCT offers the theoretical benefit of replacing the autoaggressive immune system and utilizing the hypothesized 'graft vs autoimmunity' effect, analogous to the established curative graft vs leukaemia phenomenon. Case reports so far both support [22] and refute [23] this concept, and phase I/II studies are being planned [24]. Allogeneic HSCT has become less acutely toxic due to the introduction of non-myceloablative conditioning regimens (erroneously referred to as 'mini-transplantation'), but the limited

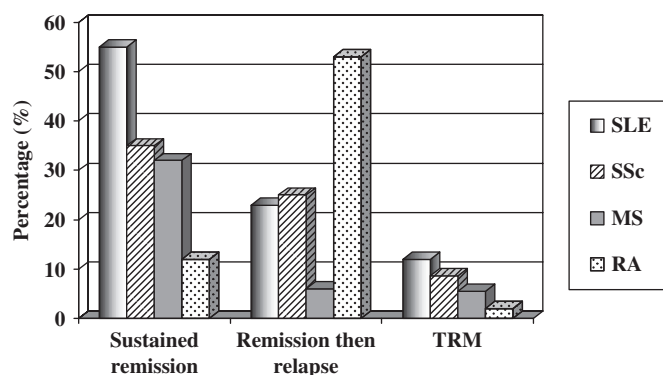


FIG. 1. Selected outcomes post-autologous HSCT in four autoimmune diseases. The selected outcomes of sustained remission, remission then relapse and treatment-related mortality are compared and contrasted between four different autoimmune diseases undergoing HSCT; SLE ($n = 53$), SSc ($n = 57$), MS ($n = 85$) and RA ($n = 73$).

availability of matched donor (siblings) puts constraints on wider application of this modality. In addition, chronic graft *vs* host disease (GvHD) remains a risk [25] with TRM ranging from 10–35%.

Prospective controlled trials (Tables 2 and 3)

Building on the experiences from pilot studies, initiatives were taken in Europe and the US to further investigate the therapeutic value of HSCT in AD through prospective, multicentre trials. The first of these, the ASTIS trial [8], was launched in 2001 under the auspices of EBMT/EULAR to compare safety and efficacy of HSCT *vs* conventional pulse therapy cyclophosphamide in patients with severe SSc at risk of early mortality (Fig. 2). Further details are available on the website (www.astistrial.com). At the time of this writing (December 2005), 62 patients from 20 European centres have been randomized to either HSCT ($n=28$) or the control arm ($n=34$). No unexpected toxicities or treatment-related mortality have been observed so far in either arm.

The North American counterpart of the ASTIS trial, sponsored by the National Institutes of Health (acronym 'SCOT', for 'Scleroderma: Cyclophosphamide or Transplantation'), is now underway to compare safety and efficacy of a different transplant regimen *vs* i.v. pulse therapy cyclophosphamide (K. Sullivan, personal communication). The protocols of ASTIS and SCOT are matched with respect to entry criteria, study parameters, endpoints and control arm to facilitate future analyses. Long-term follow-up of patients from these trials is crucial, in order to monitor potentially late sequelae or discover delayed diverging trends in (event-free) survival. Prospective trials in SLE, MS,

chronic inflammatory demyelinating polyneuropathy (CIDP) and Crohn's disease are in progress or being planned.

The prospective clinical trials will ultimately determine whether HSCT yields sufficient clinical benefit to warrant further trials to enhance its efficacy and/or improve safety. These could address open issues such as the role of post-transplant immunosuppression, timing of HSCT, constituents of the conditioning regimen (e.g. myeloablative *vs* non-myeloablative agents) or focus on more experimental issues, e.g. adoptive cellular therapy (see subsequently). It is essential that such studies are conducted within the frame of collaborative (inter)national networks, such as EBMT/EULAR.

Immune reconstitution and markers of autoimmunity

The profound degree of immunosuppression attained with HSCT has provided unique insights in the dynamics of the reconstituting immune system in relationship with the disease course. Nevertheless, interpretation is difficult in autologous settings because the sources of mature lymphocytes cannot be discerned (e.g. reinfused *vs* residual stem cells, or expanded lymphocytes). Some patterns have emerged though: specific autoantibodies did not disappear after HSCT despite long-term remissions. This has been consistently observed for Scl-70 autoantibodies in scleroderma patients, indicating that these autoantibodies were produced by non-dividing long-lived plasma cells. Titres of rheumatoid factors dropped in RA patients after HSCT, but failed to normalize and returned to pre-treatment levels before relapses, in keeping with data from RA patients treated with rituximab [26]. In SLE patients, anti-nuclear antibody (ANA) and anti-double stranded DNA (ds-DNA) antibodies disappeared in

TABLE 2. Currently running and planned prospective studies—European-based trials

Disease	Trial design	Acronym and website	Status	Safety data	Principle investigator(s)
SSc	HSCT <i>vs</i> monthly Cy IVI X 12 (Fig. 2)	ASTIS www.astistrial.com	62 randomized	No TRM	J van Laar D Farge A Tyndall G Mancardi
MS	HSCT (BEAM*/ATG/unmanipulated graft) <i>vs</i> mitoxantrone	ASTIMS www.astims.org	11 randomized	No TRM	S Bingham P Emery C Hawkey
RA	Mobilize all then HSCT (Cy/unmanipulated graft) <i>vs</i> best available	ASTIRA	Suspended (slow recruitment)	No TRM	
Crohn's	Mobilize all (Cy) then HSCT (Cy/ATG/unmanipulated graft) <i>vs</i> best available & HSCT in 1 yr	ASTIC study	Launch Q1 2006	–	
CIDP	HSCT all (Cy/ATG/unmanipulated graft) (prospective, non-randomized study)	–	Planning	–	M Kazmi R Hughes A Steck D Farge D Jayne
SLE	All HSCT (Cy/ATG/unmanipulated graft) then: randomize to immediate <i>vs</i> 'on relapse' maintenance	ASTIL	Planning	–	

Cy, cyclophosphamide.

TABLE 3. Currently running and planned prospective studies—US based trials

Disease	Trial design	Acronym and website	Sponsor and status	Safety data	Principal investigator
SLE	HSCT (Cy/ATG/CD34 selection) <i>vs</i> best available	LIST ClinicalTrials.gov	NIAID/NIH- To begin March 2006	To begin March 2006	RK Burt
SSc	HSCT (Cy/Rad/ATG/CD34 selection) <i>vs</i> monthly Cy pulses	SCOT ClinicalTrials.gov	NIAID/NIH- Recruiting	No TRM	KM Sullivan
MS	HSCT all (BEAM*/ATG/CD34 selection) (prospective single arm)	IVI X 12 www.sclerodermatrial.org HALT MS ClinicalTrials.gov	NIAID/NIH-Supported and conducted by the Immune Tolerance Network (ITN)- To begin March 2006	To begin March 2006	RA Nash

Cy, cyclophosphamide.

*BEAM = BCNU (carmustine), etoposide, cytarabine and melphalan.

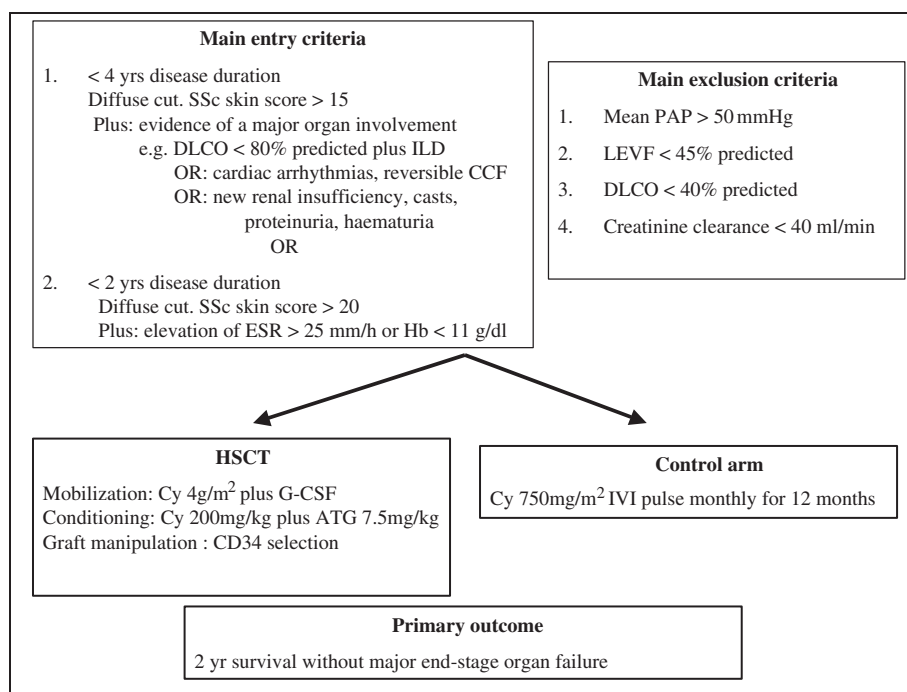


FIG. 2. Design of the ASTIS trial. The Autologous Stem cell International Scleroderma (ASTIS) trial design. Further details concerning selection criteria and outcome endpoints are available on the website <astistrial.com>.

many patients after SCT and returned to detectable levels during relapse [27]. HSCT has been shown not only to affect B-cell populations, but also to profoundly influence the T-cell compartment, as illustrated by the normalization of the dysregulated T-cell receptor (TCR) repertoires in MS [28] and SLE patients. The fact that the AD did not return despite full reinstatement of the immune repertoire gives hope that a resetting may indeed be possible with autologous HSCT [28].

In contrast, in RA patients, analyses of synovial tissue-infiltrating lymphocytes suggested that relapses originate from lesional T-cells that were not eliminated by immunoablation [29]. In JIA, the numbers of functionally active CD4+ CD25+ regulatory T-cells increased after SCT, proving that HSCT restores immunoregulatory mechanisms [30]. Clearly, future clinical studies need to be supported by experimental protocols which evaluate mechanistic aspects.

Mesenchymal stem cell (MSC) immunomodulation of autoimmune disease

MSCs have attracted attention in the past years in the areas of tissue engineering, as vehicles for gene therapy, as support cells for haematopoietic stem cell engraftment and as anti-proliferative and immunomodulating cells. The latter properties only are the subject of this review. Unlike HSCT, in which the stem cells are providing support during aplasia and haematopoietic reconstitution, MSCs may be actually therapeutic themselves.

Due to a lack of standardization concerning definition and expansion characteristics, most studies probably involve a heterogeneous group of related cell types. A recent consensus statement from the International Society of Cellular Therapy (ISCT) advocated the name 'multipotent mesenchymal stromal cell' [31], since a true stem property has not yet been proven. This means that MSCs have not yet been shown to have indefinite self-replicative ability and give rise to more than one type of mature daughter cell nor have they been proven capable of regenerating or maintaining a whole tissue compartment, thus, fulfilling all expectations of a true stem cell. However, the popular initials 'MSC' may still be used.

The MSCs are multipotent cells capable of differentiating *in vitro* and *in vivo* to different MSC lineages, including adipose, bone, cartilage and myeloid-supportive stroma [32–35]. They have been isolated from bone marrow aspirates, synovium, fat, muscle and cord blood, and while no unique marker has been identified, they are defined by a constellation of characteristics *in vitro*. MSCs are isolated from other bone marrow-derived cells by adherence to plastic and consecutive passage after which they proliferate to fibroblast-like cells in confluent cultures. They cannot be mobilized from the marrow as can haematopoietic stem cells.

They have been further defined by using a combination of phenotypic markers and functional properties. Controversy still exists over the *in vivo* phenotype of MSCs: however, *ex vivo* expanded MSCs do not express the haematopoietic markers CD34, CD45 and CD14 [35, 36]. In addition to their at least tri-lineage potentiality (fat, bone and cartilage), they can be identified as cells that stain positive for CD29, CD73, CD90 (Thy-1), CD105 (endoglin) and CD166 by flow cytometry [34–38]. Some of these surface receptors are receptors for extracellular matrix proteins and participate in 'homing' to distressed tissues [39].

Regardless of whether or not MSCs are true stem cells, clinical benefit from MSC may not require sustained engraftment of large numbers of cells. It is possible that a therapeutic benefit can be obtained by local production of growth factors and a provision of temporary paracrine anti-proliferative and immunomodulatory properties.

MSCs rapidly expand more than 1 billion-fold when cultured *in vitro*. They secrete cytokines important for haematopoiesis and have the capacity to maintain and expand lineage-specific colony-forming units from CD34+ marrow cells in long-term bone marrow culture [40–42]. MSCs are not immunostimulatory *in vitro*. They do not induce lymphocyte proliferation when co-cultured with allogeneic lymphocytes nor are they targets for CD8+ cytotoxic lymphocytes or killer immunoglobulin-like receptor-ligand mismatched natural killer (NK)-cells [43–46].

Both CD4+ and CD8+ lymphocytes bind to MSCs and the affinity is increased for activated T-cells [39]. Several adhesion molecules expressed by MSCs are essential for the interaction with

T-cells. Vascular cell adhesion molecule (VCAM) 1, intercellular adhesion molecule (ICAM)-2 and lymphocyte function-associated antigen 3 (LFA 3) are present on unstimulated MSCs, whereas the expression of ICAM-1 is inducible [35, 36, 39, 43].

In vitro results indicate that MSC possess immunosuppressive properties. Rodent, baboon and human MSCs suppress T- and B-cell lymphocyte proliferation in mixed lymphocyte cultures (MLC) or induced by mitogens and antibodies in a dose-dependant fashion [43, 45–51]. The suppression is major histocompatibility complex (MHC)-independent and in human cell cultures, the magnitude of suppression is not reduced when the MSCs are separated from the lymphocytes in transwells, indicating that cell–cell contact is not required [43, 46, 52].

In some experiments, the T-cells do not become apoptotic or anergic because they can be restimulated if MSCs are removed [49, 53, 54], but in some others irreversible cell cycle arrest in G0/G1 is seen [51], and yet in some others, apoptosis is observed [55]. MSCs reduce the formation of cytotoxic lymphocytes and NK-cells in MLC and favour the differentiation of CD4+ T-cells with presumed regulatory activity, co-expressing either CD25 or CTLA4 [52, 54]. Co-culture of purified subpopulations of immune cells with human MSCs showed that the cytokine secretion profile of dendritic cells, naïve and activated T-cells and NK-cells was altered to a more anti-inflammatory or tolerant phenotype [56]. MSC caused Th1 cells to decrease interferon- γ (INF- γ) secretion while Th2 cells increase their expression of interleukin-4.

The mechanisms underlying the immunosuppressive effect remain to be fully clarified. Soluble factors may be involved and the addition of anti-HGF and anti-TGF- β 1 partially restored the proliferation of CD2+ cells in the presence of major histocompatibility complex (MHC) [46]. Aggarwal and Pittenger [56] suggested that MSC-produced prostaglandin E₂ accounted for reduced lymphocyte proliferation. Another study suggests that indoleamine 2,3-deoxygenase-mediated tryptophan depletion by MSCs can act as a T-cell inhibitory effector mechanism [57], as has been shown for dendritic cells (DCs) [58]. Indoleamine 2,3-deoxygenase, which is induced by INF- γ , catalyses the conversion from tryptophan to kynurenine and inhibits T-cell responses. However, in the hands of Tse *et al.* [43], neither MSC production of IL-10, transforming growth factor- β 1 (TGF- β 1) and prostaglandin E₂ nor tryptophan depletion in the culture medium was responsible for the immunosuppressive effect.

This controversial data may be due to the use of MSCs generated by different techniques; the use of different stimuli, culture conditions, doses and kinetics as well as different lymphocyte populations tested. Such differences may in turn affect cytokine and chemokine secretion, with seemingly contradictory results. In addition, species-specific differences, particularly between murine and human MSCs, add to the confusion [48].

In vivo results

An immunosuppressive effect of MSC *in vivo* was first suggested in a baboon model, where infusion of *ex vivo*-expanded donor or third-party MSC delayed the time to rejection of histoincompatible skin grafts [49]. MSCs also down-regulate bleomycin-induced lung inflammation and fibrosis in murine models, if given early (but not late) after the induction [59]. MSCs adopt an epithelial-like morphology. Notably, the fact is that the epithelial crosstalk with endothelium via integrin $\alpha_v\beta_6$ controls alveolar flooding [60]. A similar effect was seen in a murine hepatic fibrosis model (carbon tetrachloride induced) using a MSC line bearing the fetal liver kinase-1 (FLK-1) marker [61]. This is a transmembrane tyrosine kinase found on endothelial cells and haematopoietic progenitors. Its ligand has been characterized as the vascular endothelium growth factor (VEGF) [62]. As with the mouse lung fibrosis model, MSCs assumed an epithelium-like morphology and expressed low levels of albumin as a hepatocyte marker.

Treatment was only effective early and not 1 week after the damage onset.

Tissue protective effects were also seen in a rat kidney model of ischaemia/reperfusion injury in which syngeneic MSCs, but not fibroblast were used [63].

Animal models of autoimmunity

Three reports of autoimmune animal model responses have recently appeared. In the two experimental allergic encephalomyelolithis (EAE) murine models, both clinical and histological improvement occurred. The responses were dependant on the time of MSC treatment, the earlier the better, and were reversed with IL-2-treatment, indicating that anergy rather than apoptosis had occurred [64, 65]. However, in a murine model of arthritis, collagen-induced arthritis (CIA) was not improved by the addition of MSCs and the *in vitro* immunosuppressive effects were reversed by the addition of tumour necrosis factor-alpha (TNF- α). MSCs were not found in the joints [66].

Human experience

Ex vivo-expanded MSC have been infused in several phase 1 studies [67–71]. No adverse events during or after MSC infusion have been observed and no ectopic tissue formation has been noted. After infusion, MSCs remain in the circulation for no more than an hour [70]. Although durable stromal cell chimerism has been difficult to establish, low levels of engrafted MSCs have been detected in several tissues [68, 71, 72].

It is possible that sufficient therapeutic benefit is obtained by local paracrine production of growth factors and the provision of a temporary anti-proliferative and immunosuppressive effect by MSC infusion. Infusion of haploidentical MSC to a patient with steroid resistant severe acute GvHD of the gut and liver promptly improved liver values and intestinal function [73]. Upon discontinuation of cyclosporine, the patient's acute GvHD recurred, but was still responsive to a second MSC infusion. Lymphocytes from the patient, when investigated on multiple occasions after MSC infusion, continued to proliferate against lymphocytes derived from the haploidentical MSC donor in co-culture experiments. This suggests an immunosuppressive effect of MSC *in vivo*, rather than the development of tolerance. The EBMT is currently planning studies employing good manufacturing practice (GMP) standard MSC expansion protocols for prevention and treatment of acute GvHD through the Stem Cell Subcommittee (W. Fibbe, K. Le Blanc, F. Frassoni, personal communication).

In conclusion, MSCs appear capable of inducing anti-proliferative, anti-inflammatory and immunomodulatory effects in activated target cells and animal models of AD, while failing to either incite or be subject to immunological reactions across allogeneic barriers. Further *in vitro* studies in humans are ongoing as are animal models of AD. The early results in human acute GvHD and apparently low toxicity may justify further studies in severe ADs.

Summary

The past decade has seen the introduction of many agents, especially biologics, which have allowed a more successful control of AD manifestations. However, the elusive aim of tolerance induction has not yet been achieved. It could be that through harnessing the complex and multifaceted potential of cellular-based therapies, especially HSCT, a 'resetting' of autoaggressive immune reactions while maintaining protective immunity will be possible. In addition, the anti-proliferative and immunomodulatory properties of MSCs combined with their immunological privilege and seemingly low toxicity may offer a new strategy for

controlling and protecting vital organs from inflammatory, destructive autoimmune reactions.

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