Mesenchymal stem cells in the treatment of autoimmune diseases

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Mesenchymal stem cells (MSCs), more accurately called multipotent mesenchymal stromal cells, are being increasingly used in the treatment or amelioration of inflammatory and ischaemic conditions, including autoimmune diseases.[1] This developed from the observation of the in vitro antiproliferative properties of MSCs, involving soluble factors and cell–cell contact-dependent events first observed in mixed lymphocyte reactions.[2] Currently there are data involving nearly all known immune competent cells showing an antiproliferative and/or cell survival effect derived from MSCs,[3] in some cases involving crosstalk and gene expression reprogramming.[4] In addition, a plethora of animal model data have mostly been positive, but not all: notable exceptions being some rodent collagen induced arthritis models[5] and murine *systemic lupus erythematosus* (SLE).[6]

The first use of MSCs in humans was as graft enhancing agents in patients with malignancies receiving haematopoietic stem cell transplants.[7] An amelioration of acute graft versus host disease (GvHD) was observed, leading to successful targeted use of MSCs for acute GvHD.[8] Due to their low acute toxicity and apparent immune privilege (allogeneic MSCs neither induce nor are subject to immune reaction), and relative ease of availability (eg, bone marrow, adipose tissue, placental products) and ex vivo expansion, the clinical application has rapidly expanded in recent years, including acute ischaemic injury such as myocardial infarct.[9] The original simplistic concept of MSCs transdifferentiating into healthy functional cardiomyocytes has been replaced by the more plausible concept that infused MSCs actively home to damaged tissue,[10] and along with other resident tissue adult stem and progenitor cells, may respond to tissue distress by producing survival and tissue protecting factors in the wound healing or inflammatory niche. However, data on postinfusion and survival of MSCs are scarce.

Although over 1000 humans have received MSCs therapeutically[11] and over 90 clinical trials are registered (http://www.clinicaltrials.gov), there is a surprising lack of convincing phase III randomised trial placebo controlled data confirming their efficacy. Single case reports and small patient series have reported positive and negative outcomes (table 1). In addition, most of the reported cases had complex clinical settings for example acute GvHD with multiple organ involvement and a multiplicity of concomitant therapies.

With regard to SLE, four patients with nephritis improved in one centre after a single infusion of allogeneic bone marrow derived MSCs.[12] The same group recently published 16 SLE cases treated with umbilical cord derived MSCs, with similar positive outcomes. In another report, two patients received autologous MSCs and experienced no effect on disease activity despite increasing regulatory T cell (Treg) levels in the blood and inhibition of lymphocyte proliferation in vitro.[13] These discrepant results could be explained by the fact that, at least in vitro, the antiproliferative effect of MSCs depends on (a) 'licensing' factor(s) released by proliferating lymphocytes, suggesting that the most appropriate clinical indications for MSCs could be acute inflammatory conditions. Alternatively, MSCs derived from patients who are ill may not be as immunosuppressive as healthy ones, though this was not the case in vitro in other studies.[14 15]

In this month's issue of *Annals of the Rheumatic Diseases*, Sun *et al*[12] report a positive outcome in 15 patients with active SLE, 14 of whom having nephritis and including the previously published 4 cases. Patients refractory to conventional treatment, including intravenous cyclophosphamide (IVCY) in 14 cases (cumulative dose: 4.8–28.8 g; treatment duration: 6–36 months), received a small dose of allogeneic bone marrow derived MSCs (1×10^6/kg by intravenous injection). Prednisolone was tapered from week 2 onwards and IVCY was continued with larger intervals. Rapid and sustained improvements in autoantibody levels, proteinuria and non-renal manifestations of SLE were reported in all cases, with no significant acute toxicity. Mean follow-up was 17 months and 1-year data were available for 13 patients. No renal biopsy data are provided. Although this report introduces another potential and acutely non-toxic therapeutic option for patients with renal lupus, many questions remain unanswered. What mechanisms

Table 1 Published clinical experience of MSC immune modulation

Autoimmune disease	Patients (N)	MSC product	Route	Outcomes	References
Acute GvHD	1	Allogeneic bone marrow	IVI	Improved skin, gut and liver	Le Blanc *et al*[20]
Acute GvHD	55	Allogeneic bone marrow	IVI	30 Improved	Le Blanc *et al*[8]
Scleroderma	1	Allogeneic bone marrow	IVI	Improved	Christopeit *et al*[21]
Multiple sclerosis	10	Allogeneic bone marrow	Intrathecal	Mixed responses	M[22]
Multiple sclerosis	3	Mixed allogous and autologous fat	Mixed IVI and intrathecal	Improved clinical findings, MRI unchanged	Mohyeddin Bonab *et al*[23]
Crohn's fistulae	4	Autologous fat	Intrafistula	75% Closure	Riordan *et al*[24]
Lupus nephritis	4	Allogeneic bone marrow	IVI	Improved SLEDAI and proteinuria	Sun *et al*[12]
Lupus nephritis	16	Allogeneic umbilical cord	IVI	Improved SLEDAI and renal function	Sun *et al*[25]
Systemic lupus erythematosus	2	Autologous bone marrow	IVI	No change	Carrion *et al*[13]

GvHD, graft versus host disease; IVI, intravenous injection; MSC, mesenchymal stem cell; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

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underlie such a prompt clinical and biological response, only 1 week after MSC injection? In severe lupus nephritis (half of the patients reported were nephrotic), proteinuria mostly decreases over a time period of several months,[16] unless antiproteinuric treatment is added (no data are provided in this respect). What pathological changes are observed on repeat kidney biopsy after MSC treatment? This pivotal issue could provide some perhaps new mechanistic insights. Does MSC treatment influence renal outcome in the long term? We know from previous studies that most drugs used to treat lupus nephritis are merely efficacious in the short term and that potential differences between treatment regimes are sometimes unmasked only after a (very) long follow-up.[17] Does MSC treatment (even repeated courses) prevent renal relapses? This would be a step forward, as recurrence of renal disease is common (35%) in lupus nephritis and negatively impacts long-term renal outcome.[18] These questions, together with many others, need to be addressed.

In terms of safety and feasibility, MSC treatment, as with all cellular treatments, poses an extra burden of product quality and good manufacturing practice standards in order to be able to compare various clinical trials. The optimal MSC source, for example bone marrow, adipose tissue or placental product, has not been established, including the issue of allogeneic versus autologous and expansion conditions. Growth factors such as fibroblast growth factor may induce rapid expansion of MSCs ex vivo, but also induce major histocompatibility complex class II expression and aneuploidy,[19] the long-term safety of which is unclear.

Finally, as the authors state, only large randomised controlled trials will establish the place, if any, for MSC treatment of autoimmune and other disorders. In the current regulatory environment this poses major logistic and financial hurdles demanding interdisciplinary and, most likely, non-commercial, investigator-initiated studies, but is being planned under the auspices of a European League Against Rheumatism stromal cell translational group strategy. A plethora of case reports and small, uncontrolled studies will not move the field forward.

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