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Mesenchymal Stromal (Stem) Cells to Improve Solid Organ Transplant Outcome: Lessons from the Initial Clinical Trials

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Abstract

Purpose of review—Discuss the recent progress on the clinical use of Mesenchymal stromal (stem) cells (MSC) in solid organ transplantation (SOT).

Recent findings—Tissue repair and immunomodulatory properties have been recognized for MSC obtained from different human tissues. MSC-based therapy has been proposed to reduce ischemia-reperfusion injury and to promote immune tolerance. The results of recent clinical trial support the safety and promising effects of autologous and allogeneic MSC in SOT. Collectively, the use of MSC in recipients of living donor kidney transplantation (LDKT) was associated with improved graft function, reduced rejection, ability to omit induction and/or lower maintenance immunosuppression regimen, as well as to treat rejection episodes.

Summary—We are living very exciting times with the implementation of novel clinical trials aimed at establishing safety, feasibility and efficacy of cellular therapies including MSC to improve SOT outcomes. The results of the initial clinical trials support the safety of MSC-based therapy and justifying cautious optimism for the immediate future.

Keywords

Mesenchymal Stem Cells (MSC); Mesenchymal Stromal Cells (MSC); Bone Marrow; Adipose Tissue; Solid Organ Transplantation (SOT); Cellular Therapies; Regenerative Medicine; Living-

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Donor Kidney Transplantation (LDKT); Clinical Trial; Ischemia/Reperfusion Injury; Acute Cellular Rejection (ACR); Immunomodulation; Immune Tolerance; Immunosuppression; Opportunistic Infections

Introduction

Transplanting cells, tissues and organs aims at the long-lasting restoration of function lost to genetic defect, inflammation, toxicity, or trauma. Cellular therapies are emerging as therapeutic options to ameliorate, reduce, modify, correct and cure medical conditions. Mesenchymal stromal (stem) cells (MSC) are particularly appealing because of their tissue repair and immunomodulatory potential (1). Herein, we review and discuss the recent progress on the clinical use of MSC in solid organ transplantation (SOT)(2-10).

Rationale for the use of MSC in solid organ transplantation

MSC comprise a heterogeneous cell population of putative pericytic origin (11-13). The 2006 guidelines of the *International Society for Cellular Therapy* (ISCT) identify MSC based on: (i) adherence to plastic; (ii), 95% of the MSC population must express CD105, CD73 and CD90; must lack expression 2% positive of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II); and (iii) multipotent differentiation (osteoblast, adipocyte and chondroblast under standard *in vitro* differentiating conditions)(12). *Bona fide* MSC are obtained from bone marrow (BM), adipose tissue (AT), umbilical cord (UC), and other human tissues (14-17), likely due to their perivascular (pericyte) origin (18-20).

Autologous MSC are obtained from the patient's own tissues or from HLA-identical siblings. *Allogeneic* MSC are obtained from 'donor-specific' (if also donate the solid organ) or 'third-party' HLA-matched/mismatched individuals (**Figure 1**). MSC are obtained in adequate numbers prior to transplantation from either a prospective living donor or from the recipient and used fresh or cryopreserved. Third-party (off-the-shelf) allogeneic MSC may represent a practical choice if other options are unavailable.

Ischemia-reperfusion injury (IRI) of SOT is the result of hypoxia-mediated cellular death and activation of stress-induced signal transduction pathways in vascular endothelium and organ parenchyma, which are triggered by cerebral or cardiac death and organ preservation, and after reperfusion. Consequences of IRI include delayed function and primary non-function, heightened organ immunogenicity due to increased expression of major histocompatibility complex (MHC) molecules, pro-inflammatory mediators, and activation of adaptive immunity. In fact, deceased donor organs have higher rates of rejection than living-donor organs (21, 22).

After inoculum, MSCs preferentially home at the site of vascular damage or inflammation where they likely function as the native resident pericytes/MSCs do in small, minor injuries (23, 24). This property may help mitigating IRI (25, 26), rescuing marginal donor organs, reducing activation of innate immunity leading to progressive tissue fibrosis, and blunting 'danger signals' that could synergize with immune tolerance-inducing strategies (**Table 1**).

Immunosuppressive protocols generally combine agents, including lymphodepletion [*i.e.*, rabbit anti-lymphocyte globulin (RATG), anti-CD25 antibody (targeting the interleukin-2 receptor), anti-CD52 antibody (campath-1H, alemtuzumab), anti-CD3 antibody, amongst others], calcineurin inhibitors (CNI: cyclosporine A, CsA; and tacrolimus), molecular target of Rapamycin (mTOR) inhibitors (sirolimus and everolimus), purine/pyrimidine synthesis inhibitors (mycophenolate mofetil–MMF; mycophenolic acid–MPA; azathioprine–AZA), cyclophosphamide (CyP), and/or steroids, amongst others. Immunosuppression heightens the risk of opportunistic infections (OI) and organ toxicity (which may progress to end-stage failure)(27, 28), and may affect quality of life of transplanted patients, as well as graft survival. Achieving permanent acceptance of transplanted tissues reproducibly without the need for life-long anti-rejection therapy represents the ‘Holy Grail’ of transplant immunobiology, and has been reported only sporadically or in limited patient cohorts (29-34).

Immunomodulatory effects of MSC have been recognized on T, B, Natural Killer (NK), dendritic (DC), and monocyte cell functions, as well as on the induction of ‘regulatory’ immune circuits (35-38). Bartholomew *et al.* described the immunomodulatory properties of MSC in allogeneic nonhuman primate skin grafts (35). LeBlanc *et al.* demonstrated that BM-MSC administration, irrespective of the HLA matching of the MSC donors, effectively treats severe graft-versus host disease (GVHD) refractory to steroids in hematopoietic stem cell (HSC) transplant recipients (39, 40). In SOT, MSC treatment may help reducing the burden of immunosuppressive regimen, treat rejection episodes, and promote induction of immune tolerance (**Table 1**)(36-38).

Clinical trials of MSC and SOT

Multiple MSC clinical trials in SOT are registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (**Table 2**)(3, 5, 7, 8), but the overall worldwide number is likely higher (4, 9). The results from recent MSC trials in SOT are encouraging (**Table 3**).

Vanikar *et al.* (2) first reported the use of donor-specific AT-MSC as part of a non-randomized protocol aimed at the induction of donor hyporesponsiveness in 100 recipients of Living Donor Kidney Transplantation (LDKT) for end-stage renal disease (ESRD). Treatment included: donor-specific leukocyte transfusion (DST; days -27,-25); anti-CD20 antibody (Rituximab; 6mg/kg, Day -18; RATG (1.5mg/kg, day -17); unmodified donor-marrow HSC (200ml, day -16); nonmyeloablative conditioning with total body irradiation (TBI; targeted to subdiaphragmatic lymph nodes, spleen, pelvic bones and lumbar vertebrae; 200CGy x5 days); intra-portal (IP) infusion of donor-specific AT-MSC, 10-day cultured BM cells, and peripheral blood stem cells (PBSC; G-CSF mobilization in the prospective donor; day -9); methylprednisone (500mg IV, days -1,0,+1); CNI (CsA 3mg/kg/day) plus prednisone (20mg/day) for first trimester, then AZA plus prednisone (5-10mg/day). Control subjects (n=100) received the same treatment without AT-MSC. The AT-MSC group displayed improved graft survival, sustained chimerism levels using low-dose immunosuppression than controls over an 18-month follow-up period. Similar outcomes over a 4-year period were observed in a subsequent large-scale, nonrandomized LDKT trial (patients declining HSC/MSC protocol enrolled as controls)(4) testing the induction of

hyporesponsiveness protocol with donor-specific AT-MSc in 606 patients vs. 310 controls receiving conventional triple immunosuppression. The results of the study are promising, though lack of randomization in both studies, and lack of a group of patients receiving the conditioning without AT-MSc in the latter limits the generalization of the results.

Perico et al. tested autologous BM-MSc in two patients with end-stage renal disease (ESRD) receiving LDKT (3). One week after LDKT, intravenous BMMSc ($1.7\text{--}2.0 \times 10^6/\text{kg}$ BW) was given under conventional immunosuppression with fractionated RATG (0.5mg/kg, days 0 through 6), anti-CD25 antibody (basiliximab, 20mg intravenously pre-transplant and day 4), steroids (tapered and weaned by 1-week post-transplant), and CNI (CsA) plus MMF maintenance. Transient increase in serum creatinine was observed in both patients, who displayed good graft function at one-year. Increased frequency of $\text{CD4}^+\text{CD25}^{\text{high}}\text{FoxP3}^+\text{CD127}^-$ T-regulatory (Treg) cells and reduction of $\text{CD8}^+\text{CD45RO}^+\text{RA}^-$ T-memory cells were observed in these two patients, when compared to historical controls receiving the same immunosuppression without MSc. A subsequent pilot trial on two additional patients evaluated the impact of (i) timing of autologous BM-MSc inoculum and (ii) omission of CD25 blockade from standard immunosuppression (10). Intravenous BM-MSc ($2.0 \times 10^6/\text{kg}$ BW) was given on the day before LDKT. One patient with higher HLA haplotype mismatch developed transient elevation of serum creatinine 2-wks after transplant with pathology compatible with acute cellular rejection (ACR) that resolved after steroid pulses. *In vitro* CD8+ T cell cytolytic function appeared more suppressed to donor than to third-party antigens in both MSc recipients; response to donor antigens progressively returned to baseline, while response to third-party antigens was unaffected by immunosuppression in historical controls by 12 months. T-memory/effector cell proportions in historical controls with standard immunosuppression (plus anti-CD25 antibody) increased over time, but markedly decreased by day 7 and remained lower than pre-transplant throughout the one-year follow-up in both MSc recipients. Unlike their previous trial (3), Treg proportions appeared unaffected by MSc inoculum, except for a transient decrease soon after transplantation (10). These two pilot trials preliminarily confirmed safety and provided encouraging mechanistic observations after inoculum of autologous MSc in immunosuppressed SOT recipients (**Table 3**), though small sample size, lack of concomitant controls and of randomization limit generalizations.

Our group (**Tan et al.**) (5, 6) completed the one-year follow-up of a prospective, open-label, randomized clinical trial on 159 patients with ESRD receiving LDKT and tested the risk/benefit profile of autologous BM-MSc infusion compared to anti-CD25 antibody (basiliximab) induction therapy (5). All patients received MMF and corticosteroids. Controls (n=51) received anti-CD25 antibody plus standard dose CNI (either CsA or tacrolimus). In the two experimental arms, anti-CD25 treatment was replaced by BM-MSc inoculum ($1\text{--}2 \times 10^6/\text{kg}$ intravenously at reperfusion and day 14 post-transplant) with either standard (n=52) or reduced-dose CNI (80% of standard dose; n=52), the latter to prevent organ toxicity (41, 42). The primary outcome was one-year incidence of biopsy-confirmed ACR and estimated glomerular filtration rate (eGFR). The secondary outcome was one-year patient and graft survival and incidence of adverse events. Replacement of CD25 blockade with autologous MSc in LDKT transplant recipients did not compromise graft and patient

safety, while yielding, when compared to controls: (i) faster recovery of renal graft function during the first month post-transplant (suggesting a possible effect on IRI, a recognized risk factor for graft failure and ACR)(43, 44); (ii) lower frequency of and less severe biopsy-confirmed ACR in the first semester post-transplant (none steroid-resistant requiring RATG, vs. 7.8% in the controls); and (iii) fewer adverse events, particularly OI. One-year graft function was comparable in all groups. Similar graft survival rates with reduction of maintenance CNI therapy in LDKT recipients was previously reported only in recipients of whole or fractionated donor-specific BM cell transplantation (45) or using anti-CD52 antibody lymphodepletion (in absence of cellular therapy), though the latter increased the rates of severe OI (46). Notably, OI occurring mostly in the first two trimesters heighten mortality rates in kidney transplant recipients in China (47). Secretion by MSC of anti-microbial/immunomodulatory molecules (*i.e.*, cathelicidin hCAP-18/LL-37)(48) might have contributed, at least in part, to the significantly lower rates of OI in recipients of MSC plus low and standard CNI doses in our trial.

Peng *et al.* (7) assessed safety and efficacy of donor-BM-MSC in LDKT recipients (nonrandomized trial). All patients received induction with cyclophosphamide and steroids followed by maintenance immunosuppression with MMF and prednisone; CNI (tacrolimus) was started on day 4; the control group received standard-dose (0.07–0.08mg/kg/day; n=6), whereas the experimental group (n=6) received low dose (0.04–0.05mg/kg) along with donor 5×10^6 BM-MSC into the renal allograft artery at reperfusion, plus 2×10^6 /kg intravenously a month later. Direct MSC injection into the renal artery was uneventful. Recipients of MSC plus low-CNI dose maintained stable graft function during the one-year follow-up and displayed higher numbers of peripheral B-memory (CD27⁺) cells at 3 months. No other differences amongst study groups were observed (*i.e.*, lymphocyte phenotypes, intracellular cytokines, one-way mixed lymphocyte responses *in vitro*, chimerism, etc.).

Lee *et al.* (9) tested donor-BM-MSC in seven HLA mismatched LDKT recipients under conventional immunosuppression based on fractionated RATG (8–10 days at 1.5 mg/kg/day) with maintenance CNI, MMF and steroids. Donor-BM-MSC (1×10^6 /kg BW) intra-osseous (IO; into the recipient's right iliac bone) on the day of kidney transplantation was uneventfully. Reduction of donor-specific lymphocyte and mitogen-induced T-cell proliferation were observed in two patients, though chimerism was never detected. Donor-specific lymphocyte or T-cell proliferation and Treg priming responses were observed in few patients. Three patients displayed biopsy-proven ACR controlled well with steroid pulse therapy; one patient received Intravenous immunoglobulin (IVIG) and plasmapheresis for acute antibody-mediated rejection on day 9 post-transplantation; ACR responsive to steroids was observed at 43 days and 613 days post-transplantation; another ACR at 12 months was detected by protocol biopsy; two patients displayed borderline change without clinical signs of rejection not requiring treatment. While the study supports the feasibility of intra-BM administration of MSC, further studies should ascertain the impact of allogeneic BM-MSC on graft outcome on a larger number of study subjects and concomitant controls.

Reinders *et al.* (8) used autologous BM-MSC to treat ACR episodes and renal interstitial fibrosis and tubular atrophy (IF/TA) in six recipients of fully HLA mismatched LDKT immunosuppressed with anti-CD25 antibody (basiliximab), CNI (tacrolimus or CsA), MMF

and prednisone, under 3-month antiviral prophylaxis. Patients displaying ACR or increased IF/TA (compared to the 4-week biopsy) at the 6-month protocol biopsy were given intravenous BM-MSC ($10^6/\text{kg}$) a week apart without modifying immunosuppression. Two subjects with biopsy-confirmed allograft rejection (Banff 1A with mild IF/TA and Banff 1B, respectively) had resolution of tubulitis without IF/TA at post-MSC treatment biopsy. A BK virus-associated nephropathy occurred 21 weeks after MSC infusion and resolved without reduction of immunosuppression. A *de novo* CMV infection occurred two weeks post-MSC infusion (6 months after discontinuing prophylaxis) resolved without reduction of immunosuppression. A patient showed persistent (months) low-grade CMV viral load post-MSC infusion despite reduction of immunosuppression. Reduced *in vitro* leukocyte proliferative responses were demonstrated 12-weeks post-MSC inoculum. The potential direct effect of MSC therapy in promoting resolution of the features of rejection in clinical allogeneic renal grafts emerges from this pilot trial. Large size clinical trials with concomitant controls will be of assistance in determining the reproducibility of the positive effects of MSC treatment on graft pathology, as well as defining the actual relationship with opportunistic viral infections.

Considerations regarding the clinical use of MSC in SOT

The *methods* utilized for MSC isolation (*i.e.*, enzymatic *vs.* non-enzymatic), selection (*i.e.*, adherence to plastic, cell sorting based on surface cell markers, etc.), expansion (*i.e.*, culture media and supplements, oxygen tension, etc.), and assessment are not yet fully standardized amongst facilities and based on the anatomical source (16). Since the 2006 ISCT guidelines (12), improved criteria for MSC isolation and characterization have been proposed (49-51).

It remains to be elucidated whether *comorbidities* (*i.e.*, chronic medical conditions: diabetes, ESRD, etc.) of MSC donor and/or recipient may negatively affect efficacy and potency of the cellular products (52), and whether these effects can be reverted under the appropriate conditions (*i.e.*, *in vitro* culture and/or *in vivo* treatments)(53-57).

Multipotency and immunomodulatory properties of MSC may represent, at least hypothetically, a *safety* threat for transplant recipients who are immunosuppressed. Development of MSC-derived neoplasm is possible, though never reported in relation to MSC inoculum in humans. A meta-analysis on a sample of 1,012 MSC recipients confirmed clinical safety (58), even though heterogeneity of both medical conditions and protocols analyzed should suggest caution. Potentiation of immunosuppression by MSC may heighten risk for (*de novo* and/or reactivation) viral infections, lymphoproliferative diseases and progressive multifocal leukoencephalopathy. Common practice prophylaxis, close monitoring and careful assessment of immune and viral status of the recipients could allow for timely interventions aimed at minimizing risks.

The effects (synergy or competition) of *concomitant therapy* on MSC viability, potency and efficacy are being investigated. Preliminary studies suggest that CNI's and of mTOR inhibitors, but not purine/pyrimidine synthesis inhibitors (MMF and MPA), may interfere with the immunomodulatory properties of MSC (3, 59-62). RATG binds to human MSC in a dose-dependent fashion *in vitro* (3, 63) and this phenomenon is associated with MSC death, impaired *in vitro* immunosuppressive effects, and susceptibility to lysis by cytokine-

activated CD8+ cytotoxic cells and NKT cells (63). Human MSC exposed to serum collected from renal transplant recipients who had received RATG treatment displayed only minimal RATG binding with no impairment of *in vitro* MSC immunomodulatory effects in mixed lymphocyte reactions (3); addition of CsA, MMF or steroids to the cultures did interfere with MSC suppression of T cell responses to mitogenic stimulation with anti-CD3/CD28 antibodies *in vitro*, while synergy was rather observed with MMF (3).

The **immunogenicity** of transplanted MSC (donor-specific or third-party) may negatively impact SOT survival. Griffin *et al.* (64) collected literature evidence in support of specific cellular (T-cell) and humoral (B-cell/antibody) immune responses against donor antigens following administration of non-manipulated, interferon (IFN)- γ -activated and differentiated allo-MSCs. These important aspects deserve further studies in the clinical setting.

While overall safety of MSC therapies emerges from recent clinical SOT trials, the heterogeneity in the **design** (MSC source, route and schedule of administration, concomitant immunotherapy, and study endpoints) amongst the published clinical trials limits the possibility of meaningful comparisons at the present time.

For a widespread application of clinical MSC products, 'regional' (centralized) Cell Processing facilities or the use of off-the-shelf, 'standardized' MSC products (*i.e.*, centralized or industry manufacturing) may allow containing the costs. The remarkable financial burden imposed by the **regulatory framework** requiring proof safety and efficacy of cellular therapies under the Investigational New Drug (IND) classification before a Biological License is obtained from regulatory agencies represents an important hurdle to the transition of cellular therapies from academic initiatives into widespread clinical applications. This issue has steamed an intense debate, as elevated costs may hinder the development of potentially promising cellular therapies that could benefit humankind even beyond SOT (65).

Patients' safety is paramount. Clinical studies should be performed under ethically approved protocols and appropriate Data Safety Monitoring Board oversight. Establishment of a 'Cell Therapy in SOT' **Registry** to gather critical parameters and outcomes will be of assistance in assessing the safety and efficacy of MSC therapy in SOT and guide the design of future trials. The selection of 'standardized' tests (*i.e.*, cell product identity, potency and clinical outcomes) and endpoints to be adopted across centers would further promote the progress of the field.

Conclusion

We are living very exciting times with the implementation of novel clinical trials aimed at establishing safety, feasibility and efficacy of cellular therapies and MSC to improve SOT outcomes. The results of the initial clinical trials are quite promising supporting the safety of the procedure and beneficial effects on SOT justifying cautious optimism for the immediate future.

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Abbreviations

ACR	Acute Cellular Rejection
AT	Adipose Tissue
AZA	Azathioprine
BM	Bone Marrow
BW	Body Weight
CGy	Centigray
cGMP	current Good Manufacturing Practice
CNI	Calcineurin Inhibitor
CMV	Cytomegalovirus
CsA	Cyclosporin A
CyP	Cyclophosphamide
DC	Dendritic Cells
DSMB	Data Safety Monitoring Board
DST	Donor-Specific Leukocyte Transfusion
EBV	Epstein Barr Virus
eGFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
G-CSF	Granulocyte–Colony Stimulating Factor
GVHD	Graft Versus Host Disease
HSC	Hematopoietic Stem Cell
HLA	Human Leukocyte Antigens
IF	Interstitial Fibrosis

IFN	Interferon
IND	Investigational New Drug
IL	Interleukin
IO	Intra-Osseous
IP	Intra-Portal
IRB	Institutional Review Board
IRI	Ischemia-Reperfusion Injury
ISCT	International Society for Cellular Therapy
IV	Intra-Venous
IVIG	Intravenous Immunoglobulin
LDKT	Living Donor Kidney Transplant
MMF	Mycophenolate Mofetil
MPA	Mycophenolic acid
MSC	Mesenchymal Stromal (Stem) Cells
mTOR	molecular Target of Rapamycin
NHBD	Non Heart-Beating Donors
NK	Natural Killer
NKT	Natural Killer T cells
OI	Opportunistic Infections
PBSC	Peripheral Blood Stem Cells
RATG	rabbit Anti-Lymphocyte Globulin
SOP	Standard Operating Procedure
SOT	Solid Organ Transplantation
TA	Tubular Atrophy
TBI	Total Body Irradiation
Treg	T regulatory cell
UC	Umbilical Cord

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compared the immunomodulatory properties of clinica-grade MSC and demonstrates the different potency based on different techniques of cell isolation and expansion.]

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Key points

- Tissue repair and immunomodulatory properties have been recognized for MSC obtained from different human tissues.
- MSC-based therapy has been proposed to reduce IRI, reduce immunosuppression, treat rejection episodes and possibly induce immune tolerance.
- Initial clinical reports support the safety of MSC in SOT and reveal encouraging positive effects on engraftment, reduction of immunosuppression burden, reduction of rejection and possibly inducing immune modulation.
- MSC may represent a viable adjuvant therapy to improve clinical outcomes in SOT.

Figure 1. Sources of MSC

Possible donor:recipient combinations for MSC therapy in SOT.

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Table 1

Therapeutic Potential of MSC for Solid Organ Transplantation

Therapeutic Application
Immunomodulation
Immunotherapy induction agent
Promotion of Immune Tolerance
Treatment of Acute Rejection
Tissue Repair
Reduction/Prevention of Ischemia Reperfusion Injury
Mitigate/Counteract Drug Toxicity (?)
Contribute to Tissue Remodeling

Table 2

Registered clinical trials of MSC in solid organ transplantation (ClinicalTrials.gov)

NCT*	Title	Site	Settings	Type of MSC	MSC Inoculum	Type of Study	Start Date
00646724	Cotransplantation of islet and mesenchymal stem cell in Type 1 diabetic patients	Fuzhou, China	Islet Transplant	UC-MSC	1-2 × 10 ⁶ /kg bw simultaneous islet and MSC transplantation via hepatic portal vein	Interventional Safety/Efficacy Single Group Assignment Open Label	Jan 2008
00658073	Induction therapy with autologous mesenchymal stem cells for kidney allografts	Fuzhou, China	Living Donor Kidney Transplant	Autologous BM-MSC	1-2 × 10 ⁶ /kg bw, IV at reperfusion and day14	Interventional Randomized Safety/Efficacy Parallel Assignment Open Label	Mar 2008
00659620	Mesenchymal stem cell transplantation in the treatment of chronic allograft nephropathy	Fuzhou, China	Chronic Kidney Rejection	Autologous BM-MSC	1-2 × 10 ⁶ /kg bw, IV once a week for 4 weeks (total 4 injections)	Interventional Safety/Efficacy Single Group Assignment Open Label	May 2008
00734396	Mesenchymal stem cells and subclinical rejection	Leiden, Netherland	Kidney Rejection	Autologous BM-MSC	10 ⁶ /kg bw, IV 7 days apart (total 2 injections)	Interventional Non-Randomized Safety/Efficacy Single Group Assignment Open Label	Feb 2009

NCT*	Title	Site	Settings	Type of MSC	MSC Inoculum	Type of Study	Start Date
00752479	Mesenchymal stem cells under Basiliximab/low dose RATG to induce renal transplant tolerance	Bergamo, Italy	Living Donor Kidney Transplant	Autologous BM-MSC	2×10 ⁶ /kg bw IV	Interventional Randomized Safety/Efficacy Parallel Assignment Open Label	May 2008
01175655	A study to evaluate the potential of mesenchymal stromal cells to treat obliterative bronchiolitis after lung transplantation	Chermside, Australia	Lung Transplant	HLA identical and allogeneic (Third-party) BM-MSC ?	2×10 ⁶ /kg bw IV, twice weekly, 2 wks	Interventional Single Group Assignment Safety/Efficacy Open Label	Feb 2010
01429038	Mesenchymal stem cells after renal or liver transplantation	Liege, Belgium	Liver or Kidney Transplant	Allogeneic (Third-party) BM-MSC	1.3-3.0×10 ⁶ /kg bw day 3±2	Interventional Non-Randomized Safety/Efficacy Parallel Assignment Open Label	Feb 2012
01668576	Properties of mesenchymal stem cells in lung transplant candidates	Atlanta, USA	Lung Transplant	Autologous BM-MSC	In vitro assessment only	Observational Cohort Cross-sectional	Aug 2012

NCT*	Title	Site	Settings	Type of MSC	MSC Inoculum	Type of Study	Start Date
01690247	Human mesenchymal stem cells induce liver transplant tolerance	Beijing, China	Liver Transplant	UC-MSC	10 ⁶ /kg bw IV once every 4 weeks day 0 to 12 weeks	Interventional Randomized Safety/Efficacy Parallel Assignment Open Label	Feb 2012

Status: Recruiting Completed Unknown

* Abbreviations; BM: Bone Marrow; bw: body weight; HLA: Human Leukocyte Antigen; IV: intravenous; MSC: Mesenchymal Stromal (stem) Cell; NCT: [ClinicalTrials.gov](#) Identifier; UC: Umbilical Cord

Table 3

Effects associated with MSC therapy in recent clinical SOT trials

Observed Benefit	AE	No. Subjects (vs. control)	Follow-up (months)	Random	Setting	Type of MSC	MSC inoculum Time & Route	Immunosuppression	Reference
Minimization of Immunosuppression Reduced rejection episodes Increased hematopoietic chimerism Donor-hyporesponsiveness <i>in vitro</i>	None	100 vs. 100	18	No	LDKT	Donor-specific, Allogeneic AT-MSC	Day -9, IP or IV	DST/HST/TBI aCD20/RATG/CyP CNI/AZA/Steroids	<i>Vanikar 2011</i>
Induction of Treg Inhibition of memory T cells Donor-hyporesponsiveness <i>in vitro</i>	Elevated sCr	2	12	No	LDKT	Autologous BM-MSC	Day 7, IV	RATG/aCD25 CsA/MMF/Steroids	<i>Perico 2011</i>
Alternative to anti-CD25 blockade Reduced maintenance CNI dose Early graft function Reduced acute rejection Reduced opportunistic infections	None	102 vs. 51	12	Yes	LDKT	Autologous BM-MSC	Day 0 and 14, IV	CNI/MMF/Steroids	<i>Tan 2012</i>
Reduced maintenance CNI dose Transient increase of memory B cells	None	6 vs. 6	12	Yes	LDKT	Donor-specific, Allogeneic BM-MSC	Day 0 (1A) Day 30 (IV)	CyP CNI/Steroids	<i>Pong 2012</i>
Minimization of Immunosuppression	None	606 vs. 310	48	No	LDKT	Donor-specific, Allogeneic AT-MSC	Day 3, IV	DST/HST/TBI RATG/CyP/IVIg CNI/MMF(AZA)/Steroids	<i>Vanikar 2012</i>
Reduced tubulitis Reduced interstitial fibrosis/tubular atrophy Donor-hyporesponsiveness <i>in vitro</i>	Viral Infections	6	5	No	LDKT	Autologous BM-MSC	6 months, IV	aCD25 CNI/MMF/Steroids	<i>Reinders 2012</i>
Inhibition of memory T cells Donor-hyporesponsiveness <i>in vitro</i>	Acute Rejection	2	12	No	LDKT	Autologous BM-MSC	Day -1, IV	RATG CNI/MMF/Steroids	<i>Perico 2013</i>
Increased Tregs Donor-hyporesponsiveness <i>in vitro</i> Increased IL10 levels	Acute Rejection	7	12	No	LDKT	Donor-specific, Allogeneic BM-MSC	Day 0, IO	RATG CNI/MMF/Steroids	<i>Lee 2013</i>

*Abbreviations:

aCD20: anti-CD20 antibody (Rituximab); aCD25: anti-CD25 antibody (Basiliximab); AT: Adipose Tissue; AZA: Azathioprine; BM: Bone Marrow; CNI: Calcineurin Inhibitor(s); CyP: Cyclophosphamide; DST: Donor specific leukocyte Transfusion; HSC: Hematopoietic Stem Cells; IA: Intra-Arterial; IO: Intra-Osseous; IP: Intraportal; IV: Intra-Venous; LDKT: Living Donor Kidney Transplant; MMF: Mycophenolate Mofetil; MSC: Mesenchymal Stromal (stem) Cell ; RATG: rabbit Anti-Thymoglobulin