Review

Utilization of Mesenchymal Stem Cells in Kidney Transplantation: From Bench to Bedside

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There has been ample of preclinical and animal studies which showed efficacy and safety of using mesenchymal stem cells (MSCs) after transplantation for tissue repair, immunosuppression or tolerance induction. However, there has been a significant progress recently using MSCs in small clinical trials after transplantation. Recent results using MSCs after transplantation seem to be feasible and safe. However, there are some limitations to show the effectiveness of these cells including source, dose, timing and route of infusions. Currently, live donor kidney transplantation has been especially considered and development of recent regimes including immunosuppression drugs and MSCs administration to kidney and other organs and deceased donor transplantation would be crucial. Therefore, in this review we focused on immunomodulatory effects of MSCs that have been extensively studied to suppress various inflammatory responses in kidney transplantation.

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INTRODUCTION

Transplantation (Tx) is the treatment of choice for patients suffering from end-stage organ damage. However, chronic immunosuppression imposes substantial risks of morbidity and mortality, including nephrotoxicity and increased risk of cardiovascular diseases and diabetes. Moreover, these drugs have failed to substantially prolong long-term graft survival in the past two decades, despite a dramatic improvement in short-term graft survival. The attention of transplant community has turned to find out new approaches to achieve allograft tolerance and avoid the need for long-term immunosuppression drugs.[1]

The greatest challenge facing the field of Tx today is to increase the number of demand organs need to be transplanted. A variety of approaches have been implemented to expand donor pool including increased live donation, a national effort to expand deceased donor donation, paired donor exchange programs, national sharing models and greater utilization of expanded criteria donors (ECD).[2-4] Although donation after brain death (DBD) accounts for the majority of deceased organ donors, recently, there has been a growing interest in donors who have severe and irreversible brain injuries but do not meet the criteria for brain death. If the physician and family agree that the patient has no chance of recovery to a meaningful life, life support can be discontinued and the patient can be allowed to arrest for circulatory progress and then still donate organs (donation after cardiac death [DCD]).[5,6] These changes have led to increased use of marginal organs which can lead to poor outcomes and increase in resource utilization and cost.[7]

Cell-based therapies have been proposed as innovative approaches to repair marginal organs, minimizing ischemia reperfusion injury (IRI) and induce immune tolerance in solid organ transplantation. The hope is that administration of cells with immunoregulatory properties to

List of Abbreviations:

AD-MSC	Adipose-derived mesenchymal stromal (stem) cells
BM-DCs	Bone marrow-derived cells
BM-MSCs	Bone marrow-derived mesenchymal stromal (stem) cells
BM-MNCs	Bone marrow-derived mononuclear stem cells
BM-EPCs	Bone marrow-derived epithelial progenitor cells
CKD	Chronic kidney disease
CRF	Chronic renal failure
MSCs	Mesenchymal stem cells
ESRD	End stage renal disease
GFR	Glomerular function rate
GS	Glomerulosclerosis
hBM-MSCs	Human bone marrow-derived mesenchymal stromal (stem) cells
hCB-MSCs	Human cord blood-derived mesenchymal stromal (stem) cells
hUC-MSCs	Human umbilical cord-derived mesenchymal stromal (stem) cells
I/R	Ischemia/Reperfusion
IF	Interstitial fibrosis
IV	Intravenous

transplant recipients could tip the balance between effector and regulatory pathways, ultimately promoting the potential of the host immune system to control the immune response to the allograft. In particular, MSC is emerging as a promising cell therapy in clinical transplantation. MSC administration in experimental models of organ transplantation produced beneficial changes including lower incidence of acute rejection, decreased opportunistic infection, better estimated renal function and prevent fibrosis progression.[8-10]

Totally, given the immunological characteristics of MSCs, there has been a significant progress using different MSCs in Tx from experimental investigations to clinical trials. Also, according to latest results, it seems that MSCs Tx is feasible and safe. Therefore, in this paper, we review potential immunosuppressive and immunomodulatory properties of MSCs particularly in kidney Tx and discuss about MSCs Biology, immunosuppressive and immunoplasticity properties of MSCs and pre-conditioning and clinical studies of using MSCs in Tx.

MSCS BIOLOGY

MSCs are undifferentiated adult stem cells of mesodermal origin that were originally identified in the bone marrow (BM) stroma by Friedenstein and his colleagues.[11] MSCs have the ability to differentiate into multiple cell lineages and induce paracrine effects. International Society for Cellular Therapy (ISCT) suggested the minimal criteria for MSCs in 2006. These are plastic-adherent cells and positive for CD73, CD90 and CD105, and negative for CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules and differentiate to osteoblasts, adipocytes and chondroblasts in vitro.[12]

These cells can be easily isolated from other BM cells due to their propensity to adhere to plastic and their ability to extensively proliferate in vitro make them an attractive and popular source of stem cells to be evaluated in experiments.[13,14] These characteristics also allow for obtaining the adequate numbers of MSCs, after expansion in culture, for potential therapeutic use.[13-15] Theoretically, MSCs are able to differentiate in multiple cell lines, however it is now accepted that following in-vivo administration, their behavior is mainly restricted to mesodermal tissues.[16] Possessing immunomodulatory properties that can ameliorate inflammation and immune responses could be regarded as another property of these cells that can facilitate tolerance transplantation. Likewise, these cells have protective properties and known as renotrophic cells.[17-21]

MSCs were originally isolated from BM in addition to the wide variety of other adult tissues such as adipose.[22] In particular, adipose tissue is of interest as the collection of fat tissue is less invasive, more easily accessible for the clinician and yields higher cell numbers in comparison with BM. Adipose-derived mesenchymal stem cells (AD-MSCs) are well known for their

immunomodulatory capabilities. In particular, their immunosuppressive property is believed to allow for transplantation in immunocompetent allogeneic or even xenogeneic recipients without the use of immunosuppression. AD-MSCs have been shown to lack major histocompatibility complex-II expression and can be used as allogenic. Also, these cells have immunosuppressive effects that mediated by prostaglandin E2 hence, they are promising for the treatment of a wide range of diseases, especially immunological cases. In addition, both preclinical and clinical studies have shown that allogeneic transplantation of AD-MSCs was able to control graft-versus-host disease (GVHD).[23-27]

IMMUNOSUPPRESSIVE PROPERTIES OF MSCS

As human BM-MSCs have been proposed to maintain immunosuppressive properties and reduce inflammation, subsequently several studies have investigated and suggested a major advantage of using AD-MSCs over many other cell types for cellular therapy.[28,29] Different studies have shown in vitro lymphocytes alloreactivity suppression in mixed lymphocytes cultures through human leukocytes antigen (HLA) independent mechanisms.[30] In addition other studies have shown outcome improvement of injury in lung, renal and neural tissues in experimental animal models using intravenous administration of MSCs suggesting paracrine effects and a shift from the production of pro-inflammatory to anti-inflammatory cytokines produced by MSCs at the site of injury.[31] Different investigations have shown that several immune cells function such as T lymphocytes proliferation and dendritic cells maturation are suppressed by MSCs while other studies have identified that MSCs increase production of anti-inflammatory cytokines or induce T regulatory cells function.[32-34]

Several studies have investigated suppressive effects of MSCs on immune cells. To discuss in more details, studies showed autologous or allogenic source of MSCs could suppress proliferation of both CD4+ and CD8+ T lymphocytes which were stimulated with mitogens or specific antigens.[35] This finding indicted such MSCs mechanism is not limited by MHC.[30] In addition, other T cell function is altered by MSCs including; decreaseed pro-inflammatory factors such as, interferon gamma (INFγ), IL-2 and tumor necrosis factor-α (TNFα) together with increased secretion of IL-4 and IL-10 which are well known for anti-inflammatory effects.[36,37] Furthermore, both in vitro and in vivo study showed promote generation of CD4+CD25+ T regulatory cells by MSCs.[34] Several studies have reported the immunosuppressive effects of MSCs on other immune cells such as B cells,[38] neutrophil cells,[39] natural killer (NK) cells[40] and dendritic cells (DC).[41] A study conducted by Corcione et al.,[38] in 2006 demonstrated that proliferation of B cells which were activated with anti-immunoglobulin antibodies or cytokines could be inhibited through interaction with MSCs. However, addition of MSCs to activated B cell culture inhibited the production of IgG which is a well-known immunoglobulin secreted by plasma cells.[38] Furthermore, NK cells which are cytotoxic lymphocytes cells mainly target cells which lack or down-regulate the expression of MHC class I. It has been reported that MSCs inhibit the cytotoxicity effects of NK cells against HLA class I expression and also suppress the INFγ production by IL-2 stimulated NK cells.[42] In addition several other studies have shown immunomodulatory interaction between MSCs and DCs which are the most potent antigen-presenting cells of immune system.[28,41] In vitro study indicated inhibit maturation of monocytes and CD34+ hematopoietic progenitor cells into DCs by MSCs as demonstrated by reduced expression of cell surface MHC class II as well as decreased production of IL-12 and TNFα.[43] In general, MSCs produce many factors which promote lymphocytes suppression such as transforming growth factor (TGF)-β, hepatocyte growth factor (HGF),[44] prostaglandin E2 (PGE2),[45] inducible nitric-oxide synthase (iONS)[46] and IL-10[47] which were characterized as possible molecules responsible for immunomodulation of MSCs (Figure).

Several injection routes including systemic intravenous (iv), renal intra-artery, parenchymal subcapsular and intraperitoneal have been used in kidney Tx experiments. Intravenous administration has been widely used in clinical trials.[48] The advantage of iv method is easy access to the vein although identifying a cell injection protocol with the rate of injection, type of syringes and cell courier is challenging.[49-51] Following systemic injection, many cells entrap in the lung and a very small amount of cells home and are detectable (less than 10 %) in injured kidney.[52,53]

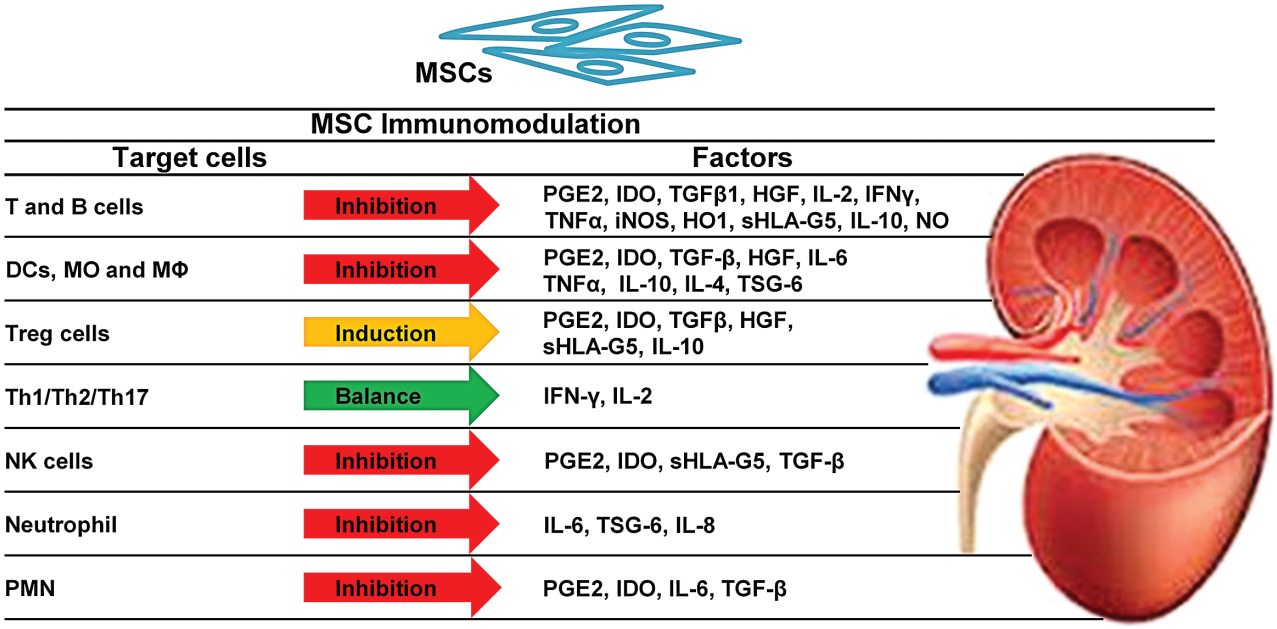

Figure. Mesenchymal stem cells have immunomodulatory properties through their paracrine effects with different mechanisms. MSCs predominantly improve renal regeneration by secretion of different growth factors, cytokines and chemokines which decrease inflammation, apoptosis, and fibrosis. MSCs: Mesenchymal stem cells; DCs: Dendritic cells; MO: Monocytes; MΦ:Macrophages; Treg cells: Regulatory T cells; Th: T helper; Nk cells: Natural killer cells; PMN: polymorphonuclear neutrophils PGE2: prostaglandin E2; IDO: indoleamine 2, 3-dioxgenase; TGFβ: transforming growth factor; HGF: hepatocyte growth factor; IL: Interleukin; TNFα: tumor necrosis factor-α; iNOS: inducible nitric-oxide synthase; HO1: haem oxygenase-1; sHLA-G5: soluble HLA-G5; NO: nitric oxide; TSG-6: TNF-stimulated gene 6 protein; IFN-γ: interferon gamma.

Various doses between 0.5-10 × 10^6 cells/kg have been used in kidney Tx experimental studies. Desired effects have not been influenced by different doses, there was neither dose depending effect using multiple cell injections nor cell product number.[54] Multiple injections may impact the long-lasting effect because the positive changes may decrease in vivo over time. Studies showed that multiple injections may be superior to single injection.

IMMUNOPLASTICITY OF MSCS AND PRE-CONDITIONING

The modulation of inflammation is a critical point in regeneration processes after many diseases. On the one hand a sufficient inflammatory response has to be created to fight microbial infections; on the other hand a sufficient inhibition of inflammatory pathways must be provided to control excessive inflammation and its harmful effects[55] that regulatory T cells are the emerging key players of immunoregulatory mechanisms and MSCs can immunomodulate these cells through different cytokines.

Therapeutic effects of MSCs may depend largely on the capacity of MSCs to regulate inflammation and tissue homeostasis via an array of immunosuppressive factors, cytokines, growth factors and differentiation factors. These include interleukin 6 (IL-6), TGF-β, PGE2, HGF, epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin growth factor (IGF), stromal cell–derived factor 1 (SCF-1), the tryptophan-catabolic enzyme indoleamine 2, 3-dioxgenase (IDO), nitric oxide (NO) and so on.[56-58] Together these secreted factors may inhibit inflammatory responses, promote endothelial and fibroblast activities, and facilitate the proliferation and differentiation of progenitor cells in tissues in situ (Figure).

However, expansion of immunotherapy with effective MSCs is hampered by lack of knowledge about the mechanisms of action and the therapeutic components of MSCs. Such knowledge allows better identification of diseases that are responsive to MSCs treatment, optimization of the MSCs production, and development of therapy based on functional components of MSCs. In order to

achieve the components that carry the therapeutic immunomodulatory activity of MSCs, further investigation is needed to allow more effective manipulation of MSC function and characterization of immunoplasticity of MSCs and pre-conditioning for clinical applications.

The IDO-MSCs inhibited the proliferation of CD4+CD25+ effector T cells to a greater extent than wide-type (WT)-MSCs. Co-culture of peripheral blood mononuclear cells (PBMNCs) and IDO-MSCs induced a higher percentage of CD4+CD25+Foxp3+ Treg cells in PBMCs. Additionally, the antigen-specific suppressive function of these CD4+CD25+ Treg cells was increased. The IDO-MSCs-treated Treg cells showed upregulated expression of cytotoxic T-lymphocyte-associated antigen 4 and increased secretion of IL-10 and TGF-β. Antigen-specific CD4+CD25+ Treg cells induced by IDO-MSCs in low doses and prolonged graft survival and induced tolerance, as evidenced by the finding that IDO-MSCs-treated kidney transplant recipients accepted donor-specific skin grafts but rejected third-party grafts.[59]

In rats with acute pyelonephritis, pro-inflammatory cytokine levels such as TNF-α, malondialdehyde, nitrite and myeloperoxidase activity were significantly increased. Histological evaluation showed numerous attributes of inflammation and tissue damage in the kidney. In this study, intravenous injection of MSCs caused a remarkable decrease of all pathologic signs in renal tissue and activated leukocytes induced pre-conditioning-like signaling in MSCs. This study showed alterations of expression or activity of inducible NO synthase, TGF-β, matrix metalloproteinase-2 (MMP2) and glycogen synthase kinase-3β (GSK3), which could mediate immunomodulation and protective effects of MSCs. This signaling could be characterized as inflammatory pre-conditioning.[60]

MSCs culture as three-dimensional aggregation or pro-inflammatory cytokine treatment increased the secretion of immunomodulatory factors. Pre-conditioning of human MSC spheroids with TNF-α and IFN-γ as pro-inflammatory cytokines resulted in more immunomodulatory activity on macrophages.[61]

Furthermore, in the similar study, after priming MSCs with pro-inflammatory cytokines such as IFN-γ plus TNF-α, these cells were less potent at increasing cytokine production by CD3 and CD28-activated PBMNCs and more effective at inhibiting T-cell proliferation but had preserved antiapoptotic functions. Without priming with pro-inflammatory cytokines (unprimed) MSCs induce a transient increase in synthesis of IFN-γ and IL-2 by activated T cells. So, pre-treatment of MSCs with IFN-γ plus TNF-α may increase their effectiveness and safety in vivo.[62]

Wharton's jelly stromal cells (WJSCs), treated or not with activation-related cytokines (Licensing) can influence the immunosuppressive action of WJSCs. Licensing of WJSCs increased the immunosuppressive effect, in both contact and non-contact settings.[63]

Liu et al. showed that initial co-culture with telomerized stromal cells in the presence of stem cell factor, flt3 ligand, and thrombopoietin, followed by co-culture on Delta-1- and -4-coexpressing stromal cells led to a higher percentage and number of pre-T cells.[64]

Treatment of MSCs with pro-inflammatory cytokines such as IL-1ß, IL-6 and IL-23 preserved the suppressive ability of allogeneic T cell proliferation and produced higher level of TGF-β and lower level of IL-4. In this study human BM-MSCs and adipose-derived MSCs (AD-MSCs) were cultured with or without IL-1b, IL-6 and IL-23 as pro-inflammatory cytokines. They concluded pro-inflammatory cytokines up-regulate the efficacy of MSCs in cell-based therapy of degenerative, inflammatory and autoimmune disorders.[65]

Inhibition of immune cells relies on a combination of factors that are not constitutively expressed by MSCs, but are induced after MSCs priming by inflammatory stimuli.[66] IFN-γ is the pivotal licensing agent for MSCs suppressive function,[67] whereas TNF-α or IL-1a/b cooperates with IFN-γ to reinforce MSCs-mediated inhibition of T-cell proliferation.[68] The specific molecular mechanisms involved in the immune regulatory properties of MSCs are still under evaluation and involve both cell contact-dependent mechanisms,[69,70] and soluble inducible factors, including IDO, PGE2, NO, heme oxygenase, galectins, HLAG5, TGF-β1, and TNF-α-induced protein 6 (TSG-6).[42,67,71-4] The immune-regulating activity of MSCs has been reported to contain major interspecies differences among the supporting molecular pathways. In particular, murine MSCs preferentially use

inducible NO synthase (iNOS), whereas IDO is the most important T-cell inhibitory system in human MSCs.[75] Therefore, it is crucial to design fully standardized and reproducible in vitro assays, including phenotypic and functional experiments, to compare qualitatively and quantitatively the immunological properties of clinical-grade MSCs. So far, such an effort of standardization has not been undertaken, leading to inconstant, not comparable, and sometimes contradictory results.

Yang et al., by a small molecule screen, identified tetrandrine as a potential activator for secretion of PGE2, a potent immunosuppressive agent, by MSCs. Tetrandrine increased MSCs PGE2 secretion through the NF-κB/COX-2 signaling pathway. In co-culture system, tetrandrine-primed MSCs attenuated the level of TNF-α secreted by mouse macrophages (RAW264.7). Systemic injection of the primed MSCs in a mouse model with ear skin inflammation compared to unprimed cells significantly reduced the level of TNF-α in the inflamed ear.[76]

Inflammation causes pain including chronic pain and it has been showed that both the cannabinoid signaling and MSCs could reduce inflammatory pain. Although, MSCs survival and differentiation are dependent on cannabinoid signaling, its role in immunomodulatory effects of MSCs on inflammation and reduce pain sensitivity is known slightly. This study, showed that mice BM-MSCs expressed both of cannabinoid receptor type 1 and 2 (CB1 and CB2) and CB2 expression level was increased in mature BM-MSCs. In addition, this study showed that tetrahydrocannabinol (THC) pre-treatment activated CB2 and ERK signaling and enhanced the immunomodulation of MSCs on inflammation-associated cytokines release from lipopolysaccharides stimulated microglia. In vivo, THC pre-treatment increased the immunomodulatory effects of BM-MSCs by reducing the release of pro-inflammatory cytokines.[77]

The expression of immunomodulatory factor PD-L1 (programmed death-ligand 1) and IDO activity were upregulated with IFN-γ and a multiple cytokine cocktail (MC) containing of IFN-γ, TGF-β and retinoic acid (RA). Consequently, both treatments enhanced the capacity of human umbilical cord-derived MSCs (hUC-MSCs) to inhibit CD4+ and CD8+ T cell proliferation and IFN-γ production. In vivo, no immunomodulation was observed by the hUC-MSCs. The majority of hUC-MSCs were trapped in the lungs after four hours intravenous infusion in mice with CCl4-induced inflammatory liver injury. Inflammatory liver slices in the ex vivo co-culture system, showed significantly increased modulatory capacity of hUC-MSCs treated with MC compared with untreated hUC-MSCs.[78]

However, MSCs can both promote an immune response and inhibit it, in accordance with the dynamics of inflammation and depending on the strength of activation of the immune system, the types of inflammatory cytokines present and the effects of immunosuppressants. Inflammation status determines the immunoregulatory fate of MSCs. However, MSCs can be rendered immunosuppressive in the presence of strong inflammation; weak inflammation paradoxically causes MSCs to enhance the immune response. In this regard, immunosuppressants such as Cyclosporin A or Dexamethasone can revert MSC-mediated immunosuppression.[79,80] In the other hand, there are some studies that shown enhancement of the immunoregulatory potency of mesenchymal stromal cells by treatment with immunosuppressive drugs.[25,28,29]

Therefore, while it is becoming clear that appropriate inflammatory stimulation is needed to elicit the immunosuppressive function of MSCs, further investigation into the underlying molecular mechanisms is needed to allow more effective manipulation of MSC function for clinical applications.

Pre-conditioning of the cells could increase homing and strengthen the potential benefit. Progenitor cells migrate to injured kidney tissue regarding homing signal. Mice MSCs home to injured tissue using CD44 and CXCR4/CXCR7 axis.[28,29] MSCs preconditioning with IGF-I could enhance the expression of CXCR4 receptor (CD184) and ultimately apply the renoprotective effects.[30] Preconditioning human cord blood-derived mesenchymal stromal cells (hCB-MSCs) in hypoxic situation may enhance angiogenic properties & anti-apoptotic potentials.[31]

CLINICAL STUDIES

MSCs preferentially home at the site of vascular damage or inflammation where they likely function as the native resident pericytes/MSCs in small,

minor injuries. This property may help mitigating IRI, 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. Immunomodulatory effects of MSC have been recognized on T, B, NK, DC, and monocyte cell functions, as well as on the induction of 'regulatory' immune circuits.[81]

Tan J[82] and his colleagues at Fuzhou General Hospital in China, studied the possibility of autologous MSCs serving as replacement of antibody induction for patients with end-stage renal disease. Both at the time of kidney reperfusion and two weeks later, patients were inoculated with autologous BM-MSCs (1-2 × 10^6/kg). Fifty three patients received standard-dose and 52 patients received low-dose CNI. The 51 patients in the control group received anti-IL-2 receptor antibody and standard-dose CNI. After 6 months, 7.5% of the autologous MSCs and standard-dose CNI group and 7.7% of the low-dose group had biopsy-proven acute rejection, compared with 21.5% of the control group. 7.8% of patients in the control group had glucorticoid-resistant rejection, while none of the patients in the other two groups showed this complication. In both mesenchymal stem cell groups, renal function recovered faster. This showed an increased eGFR level in the first month post-surgery than in the control group. The results of this study indicated that mesenchymal stem cells rather than anti-IL-2 receptor antibody induction therapy produced a lower incidence of acute rejection, lowered the risk of opportunistic infection, and after one year, improved renal function.

A study regarding the effects of MSCs in allogeneic transplant rejection and fibrosis was conducted at Leiden University Medical Center in the Netherlands.[83] Six patients received autologous BM-MSCs infusions. Two recipients had allograft rejection and received surveillance biopsies. Maintenance immunosuppression remained unaltered, while both patients had a resolution of tubulitis [mononuclear cells (MNCs) in the renal tubular wall] without interstitial fibrosis (IF) or tubular atrophy (TA). Five patients showed a donor-specific reduction of the peripheral blood MNCs proliferation assay and three patients had opportunistic viral infections. The authors concluded, that in allogeneic transplant recipients with sub-clinical rejection, IF and TA, autologous BM-MSCs treatment is feasible and beneficial.

In a study conducted at Stem Cell Biology and Tissue Engineering Center in SunYat-sen University,[84] the use of MSCs with its immunosuppressive function was studied. Donor-derived BM-MSCs along with a dose of tacrolimus were administered to six kidney transplant recipients. Six other patients serving as the control received a dose of tacrolimus. Within the 12 months post-kidney transplantation, the safety of mesenchymal stem cell infusion, acute rejection, graft function, and patient and graft survival were observed. There was no immediate or long-term toxic side effects linked with the MSCs.In the MSC recipients, the tacrolimus dose were significantly reduced in comparison with the control group. At the third month, patients in the mesenchymal stem cell group had notably higher B-cell levels than the control group. Furthermore, at the third month all of the patients had no chimerisms and at month twelve, all had stable renal function. The control group had one acute rejection. As a result, MSCs could reduce the dosage of conventional immunosuppressive drug in renal transplantation.

Perico N and colleagues[85] assessed clinical application of MSCs in transplantation. MSCs were administered intravenously 7 days after transplantation from living-related donors that were given T cell-depleting induction therapy and maintenance immunosuppression with cyclosporine and mycophenolate mofetil in two patients. This study showed that pre-transplant infusion of MSCs allows enlargement of Treg in the peripheral blood, controls memory CD8+ T cell function and protects from graft dysfunction while fostering immunoregulation.

Living-donor renal transplantation (LDRT) using pre-transplant stem cell transplantation (SCT) was performed for minimization of immunosuppression by Vanikar AV.[86] In this clinical trial, 606 patients from 916 received tolerance induction protocol (TIP) and 310 (control group) patients treated with triple immunosuppression including calcineurin inhibitor (CNI), mycophenolate mofetil (MMF), and prednisone. The test group was the TIP group. The four-year patient survival ranged from a minimum of 82.7% to a maximum of 93.5%. The mean serum creatinine (mg/dl) at 4 years ranged from 1.26 to

2.1. With these results, it can be said that stem cell transplantation is effective for minimization in LDRT.

Perico N and colleagues[87] assessed the clinical application of MSCs for immunomodulation therapy in transplantation. CD4+ FoxP3+ Treg expansion was comparable in MSCs-treated patients with or without basiliximab induction and pre-transplant MSCs did not affect kidney graft negatively. In conclusion, induction therapy without basiliximab showed no advantages on CD4+ FoxP3+ Treg expansion.

Lee H and colleagues[88] gave living adult donor kidney transplantation (LDKT) recipients MSCs derived from the donor bone marrow in order to evaluate the safety of immunological changes in relation to intra-osseous injection of MSC into the bone marrow. At the time of transplantation, donor MSC was injected into the BM of the recipient. There were no local complications or graft failure. Three recipients had biopsy-proven acute rejections. The serum creatinine was a median of 1.23 mg/dl. Plasma level of IL-10 increased in patients with Treg induction. As a result, donor MSC injection is safe and there may be a link between the induction of inhibitory immune response and the clinical outcome in the MSC kidney transplanted patients. Table 1 and 2 shows the summary of clinical studies and registered clinical trials using MSCs in kidney transplantation, respectively.

One group has recently studied the effect of allogenic human MSCs from adult BM on kidney functions in 10 renal transplantation cases. This study showed significant improvement of kidney function testes including serum creatinine and creatinine clearance in transplantation group after MSCs injection. Other recent study by Tan and his group (2012) has investigated the use of autologous MSCs as replacement for biologic agents in living-related kidney transplants in 159 patients with end-stage renal disease to reduce acute rejection.[82] This study reported that among patients undergoing renal transplant, the use of autologous MSCs compared with anti-IL-2 receptor antibody induction therapy resulted in lower incidence of acute rejection, decreased risk of opportunistic infection, and better estimated renal function at 1 year.[82] In addition, other study in 2011, investigated the safety and clinical feasibility of autologous MSCs infusion in two recipients of kidney from living-related donors. Results showed feasibility of MSCs infusion and enlargement of Treg in the

Table 1. Clinical Studies of Using MSCs in Kidney Transplantation

Author	Type of Cell Used	Type of Transplant	Number of Patients	Study Conclusion
Tan J[82]	BM-MSC	Kidney	159	Among patients undergoing renal transplant, the use of autologous MSCs compared with anti-IL-2 receptor antibody induction therapy resulted in lower incidence of acute rejection, decreased risk of opportunistic infection, and better estimated renal function at 1 year.
Reinders ME[83]	BM-MSC	Kidney	6	Autologous BM-MSC treatment in transplant recipients with subclinical rejection and IF/TA is clinically feasible and safe, and the findings are suggestive of systemic immunosuppression.
Peng Y[84]	BM-MSC	Kidney	12	These preliminary data suggest that the use of MSCs could provide potential benefits in renal transplantation by reducing the dosage of conventional immunosuppressive drug that is required to maintain long-term graft survival and function.
Perico N[85]	BM-MSC	Kidney	2	Findings from this study in the two patients show that MSC infusion in kidney transplant recipients is feasible, allows enlargement of Treg in the peripheral blood, and controls memory CD8+ T cell function. Future clinical trials with MSCs to look with the greatest care for unwanted side effects are advised.
Vanikar AV[86]	AD-MSC and HSC*	Kidney	916	Stem cell transplantation is effective in IS minimization in LDRT resulting in good graft function and patient and graft survival at 4 years
Lee H[88]	BM-MSC	Kidney	7	Donor MSC injection into the iliac bone at the time of kidney tx was feasible and safe. A possible correlation was observed between the induction of inhibitory immune responses and the clinical outcome in the MSC-kidney transplanted patients. Further research will be performed to evaluate the efficacy of MSC injection for the induction of mixed chimerism and subsequent immune tolerance.

* Hematopoietic stem cell. Iranian Journal of Kidney Diseases. www.ijkd.org

Table 2. Registered Clinical Trials of MSCs in Kidney Transplantation

NCT*	Status	Title	Site	Type of MSC	Start date
NCT02409940	Recruiting	To elucidate the effect of mesenchymal stem cells on the T-cell repertoire of kidney transplant patients	Chandigarh, India	Autologous/allogeneic; BM-MSC	September 2013
NCT02387151	Recruiting	Allogeneic mesenchymal stromal cell therapy in renal transplant recipients	Leiden, Netherlands	Allogeneic; BM-MSC	March 2015
NCT02057965	Recruiting	Mesenchymal stromal cell therapy in renal recipients	Leiden, Netherlands	Autologous; BM-MSC	March 2014
NCT02012153	Recruiting	Mesenchymal stromal cells in kidney transplant recipients	Bergamo, Italy	Autologous; BM-MSC	December 2013
NCT00659620	Unknown	Mesenchymal stem cell transplantation in the treatment of chronic allograft nephropathy	Fuzhou, Fujian	Autologous; BM-MSC	May 2008
NCT00734396	Completed	Mesenchymal stem cells and subclinical rejection	Leiden, Netherlands	Autologous; BM-MSC	February 2009
NCT00752479	Terminated	Mesenchymal stem cells under basiliximab/low dose RATG to induce renal transplant tolerance	Bergamo, Italy	Autologous; BM-MSC	May 2008
NCT00658073	Completed	Induction therapy with autologous mesenchymal stem cells for kidney allografts	Fuzhou, Fujian	Autologous; BM-MSC	March 2008
NCT01429038	Recruiting	Mesenchymal stem cells after renal or liver transplantation	Liege, Belgium	Allogeneic; BM-MSC	February 2012

*NCT: NIH clinical trials (www.clinicaltrials.gov). Iranian Journal of Kidney Diseases. www.ijkd.org

peripheral blood, and controls memory CD8+ T cell function.

CONCLUSION

There has been a significant progress using MSCs in Tx from preclinical phase to a clinical reality. Recent results have been promising and using MSCs in transplant recipients seems feasible and safe. Current studies mainly focused on live donor kidney transplantation. In this regard, potential immunomodulatory properties of MSCs to suppress numerous inflammatory responses in organ transplantation especially in kidney transplantation have been extensively shown and thus it seems that should be considered. However, there are more hurdles to overcome such as source, dose, timing and route of the infusions. On the other hand, expansion of current regimes to other organs and deceased donor transplantation would be crucial.

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