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REVIEW

Mesenchymal stem cells for kidney transplantation

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Abstract

The long term consequence of immunosuppressive therapy in kidney transplantation has prompted investigation of alternative means to modify the immune response to the allograft. Cell based therapies are potentially attractive as they may provide a long lasting immunomodulatory effect, may repair tissues and reduce the necessity to take immunosuppressive drug therapy. Of the current cell therapies, mesenchymal stem cells have now been trialled in small numbers of human kidney transplantation with apparent safety and potential efficacy. Many issues however need to be resolved before these cells will become mainstays of transplant immunosuppression including *ex vivo* modification to enhance immunomodulatory properties, cell number, route and frequency of administration as well as cellular source of origin.

Key words: Mesenchymal stem cells; Kidney transplantation; Immunosuppression; Solid organ transplantation; Cellular therapies

Core tip: This review summaries several of the most prominent cellular therapies currently being examined for use in immunosuppression. From the current evidence the reviewers make the argument that mesenchymal stem cells offer the best chance of a useful and functional cellular therapy for solid organ transplantation.

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INTRODUCTION

Kidney transplantation remains the optimal treatment for end stage renal disease (ESRD) providing excellent short term outcome with greater quality of life than that provided by dialysis[1]. Whilst short term graft survival is improving and acute rejection rates are dropping long term graft survival rates remain a major focus for clinical improvement. There are many factors that can impact the prognosis of a kidney transplant, from graft or donor considerations[2,3], factors involving the immunosuppressant regime[4,5], and issues concerning the recipient[6,7].

Tissue typing and stringent exclusion criteria are implemented pre-transplant to reduce the risk of donor related problems[3]. Issues with the recipient such as non-compliance and co-morbidity are much more difficult to manage and are often beyond a clinician's power to control[6,7].

When a suitable kidney donor is found, it is then important to make sure that the graft does not reject by suppressing the recipient's immune system. Current immunosuppressive drugs may be classified into five groups based on their mechanism of action: (1) regulators of gene expression; (2) alkylating agents; (3) inhibitors of de novo purine synthesis; (4) inhibitors of de novo pyrimidine synthesis; and (5) inhibitors of kinases and phosphatases[5]. Targeting each of these mecha-

nisms has its benefits and disadvantages and tailoring a drug schedule has the potential to impact long term graft function and the quality of life of the recipient. However all current drugs are associated with a range of adverse effects including renal toxicity, opportunistic infections, development of malignancy and metabolic complications[5]. A common trait among all these drug classes is the targeting of T cell function[5,8-10]. T cells play an important role in rejection via alloantigen recognition and the direction of an effector response that results in graft damage and dysfunction[11].

Of these issues it is the modification of immunosuppression that is an obvious place to try and improve patient outcomes, as more options will allow for customised treatment programs unique to each patients needs. Towards this end, there has been a recent increase in the development of alternative means of immunosuppression for organ transplantation. Utilizing cell-based therapies for immunosuppression is an alternative approach to traditional pharmacological methods and represents a change in paradigm for transplantation therapies.

CELL THERAPIES FOR ORGAN TRANSPLANTATION

The basic concept of cell therapy is to implant cells with desired properties into a patient in an attempt to treat or cure. Although this idea has been around since the 19th century, it was not until 1968 that it became a viable treatment with the first bone marrow transplant[12]. Since then, there has been a steady expansion in the type of cells transplanted and the conditions that can be treated. The purpose of this review is to examine the state of several cell types that are being evaluated for preclinical or early clinical trials in solid organ transplantation (SOT), including; T regulatory cells (Tregs), dendritic cells (DCs), and with a particular emphasis on mesenchymal stem cells (MSCs) which have shown the greatest progress and potential as a cellular therapy.

RGULATORY T CELLS

Tregs are naturally occurring T cells which express the cell surface markers $CD4^+CD25^+$ $FoxP3^+$ and a variety of differing cell surface markers (CD127, Helios)[13,14]. Tregs are concerned with the maintenance of immunological self-tolerance by suppressing self-reactive lymphocytes that escape clonal deletion[14]. Naturally occurring Tregs are formed from naive T cells in the thymus. However these naive T cells can be converted to Tregs *in vitro* using TGF-β induction of FoxP3[15], providing a second source of Tregs for cell therapy.

Tregs are able to suppress the immune system on many levels, combining inhibitory cytokine secretion(*e.g.*, *via* TGF-β, IL-10)[16,17], cytotoxicity and inhibition of NK cells[18,19], and direct modulation of antigen presenting cells[20-22]. This multifaceted approach to immunosuppression makes Tregs a promising therapy to facilitate long term graft survival. Recently there have been advances in the methods for Treg isolation and expansion, with large scale expansion from peripheral blood (PB), umbilical cord blood (UBC), and induced Tregs from naive peripheral blood precursors[23]. There have also been positive results from experimental animal models[24]. Of greatest interest are the clinical trials that have used Tregs as a cellular therapy in graft-*vs*-host disease (GVHD), a major and potentially lethal transplant complication that is particularly prevalent in patients who have undergone a hematopoietic stem cell transplant (HSTC)[25,26]. With generally positive outcomes from the GVHD trials[26], it is likely that we will see Tregs initially deployed as an adjunctive therapy in SOT before being used in patients who have a high risk of rejection or who have already experienced adverse effects from standard immunosuppression. This would allow for the efficacy of Tregs to be determined in a way that would be ethical and pose a minimal risk of complications.

In addition to their safety, there are several other important issues that need to be addressed in the pursuit of an effective Treg based therapy. As mentioned above, there have been advances in the isolation and expansion of Tregs. These advances go some way to addressing the large number of cells that would be required for an effective therapy, with some estimates placing the required number at 11×10^8 cells/kg[27]. Another concern is the source of the Tregs. Currently, the most appropriate source for therapy is unknown, with uncertainty focused on whether alloantigen or antibody mediated expansion is the safest and most effective method[23]. The stability of Tregs *in vivo* has also been found to be problematic with studies finding that Tregs can lose FoxP3 expression and develop an effector cell phenotype, becoming pathogenic[28]. Of relevance to the previous point about the source of Tregs is evidence suggesting that induced Tregs lose FoxP3 expression at a much higher rate than natural Tregs[29,30]. These are just a few of the issues surrounding the use of Tregs for SOT that the ONE study (www.theonestudy.org) hopes to address. Currently the ONE study is examining the use of polyclonally expanded Tregs and alloantigen driven Tregs in kidney transplantation at doses of 1, 3, 6 and 10 $\times 10^6$ Tregs/kg. As of writing this no results have been published[23].

DENDRITIC CELLS

Dendritic cells (DCs) are able to function as antigen presenting cells that drive graft rejection (immunogenic DC) or have a role in promoting graft acceptance (tolerogenic DC; TolDC) depending on their state[31]. Immunogenic DCs cause T cell activation and proliferation with the use of three signals: (1) they present antigens on MHC molecules; (2) They provide co-stimulatory molecules; and (3) they secrete pro-inflammatory molecules. Only when all three signals are present can DCs activate T cells[31]. TolDCs are also able to interact with regulatory

T cells to promote immune tolerance. The role that DCs play in immune tolerance is twofold. Firstly, they play a role in the deletion of self-reactive thymocytes in the thymus[32]. Secondly, and of relevance to transplantation, they aid in peripheral tolerance. They do this by the presentation of antigens while lacking the co-stimulatory molecules required for T cell activation[32,33]. This causes T cell unresponsiveness as well as Treg induction[33].

Two strategies for the use of TolDCs in transplantation are likely to be applied in the setting of allotransplantation. The first involves negative immunization by administering either autologous DCs that have been exposed to alloantigens or donor derived DCs, pre-transplant[34]. The second method involves the use of recipient derived DCs delivered on the day of transplantation[35]. Intravenous injection of immature DCs of either donor or recipient origin at the time of transplantation have prolonged allograft survival in SOT models[36]. There is a large amount of literature on the use of DCs in pre-clinical experimental models[36,37]. Clinical trials looking at DCs have been carried out in both type-1 diabetes[38] and rheumatoid arthritis[39]. This has shown that the use of DCs for immunomodulation is safe and effective.

Many of the issues that face Tregs are also pertinent in the consideration of DCs as a cellular therapy. Cell dose and the best method for the isolation and expansion of the cells is uncertain. The use of either recipient derived DCs or donor DCs is yet to be resolved and adding additional complexity to this issue is the question of negative immunization vs. recipient derived DCs delivered peri-transplant. Again, the ONE study aims to answer these questions and early trials of DCs in SOT are ongoing as of writing this.

MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are a multipotent cell lineage that has great potential for use in cellular therapies and is already being widely tested in clinical trials. www.clinicaltrials.gov currently lists 396 studies using MSCs in conditions such as spinal cord injury, diabetes, Alzheimer's disease, and kidney injury.

The International Society for Cellular Therapy (ISCT) has set the minimal criteria for defining MSCs as being plastic adherent, capable of differentiation into osteoblasts, adipocytes, and chondroblasts, and expressing CD105, CD73, and CD90 while lacking expression of CD45, CD34, CD14 or CD11b, CD19, and HLA-DR surface molecules[40].

MSCs are capable of being isolated from many tissues including bone, fat, and placenta. When cultured they adhere to plastic and have a fibroblast-like appearance, possessing a long, thin body and a small number of protrusions[40]. MSCs have a role in the formation and homeostasis of connective and structural tissues *via* the production of extracellular matrix, stabilization and regulation of the tissue vascularisation, and the creation of new connective tissue cells[41,42]. In addition to this, they also play a role in the immune system by inducing tolerogenic[42] properties that can be enhanced by *in vitro* treatment[43]. These roles are able to be exploited to aid in regenerative medicine and in immunosuppression. Combined with the many tissues from which they can be isolated and their ability to remain stable while being expanded *in vitro*[44] it becomes clear why so much work is now being carried out using MSCs for a large number of clinical applications.

The immunosuppressive abilities of MSCs are mediated by either nitric oxide synthase (iNOS) in mice[45,46], or indolamine 2,3-dioxygenase (IDO) in humans[46]. iNOS results in the production of nitric oxide (NO) which is an immunosuppressive agent in high concentrations[47]. Alternatively, IDO degrades the essential amino acid tryptophan thereby resulting in immunosuppression. The accumulation of the tryptophan metabolite kynurenine is also known to mediate the immunoregulatory effects of MSCs[48].

The exact mechanisms of how two pathways cause immunosuppression are not fully understood. In addition to these key factors, there are several immunosuppressive molecules secreted by MSCs. These include; PGE-2, IL-10, HO-1, PD-L1, and IL-6[49].

In reaction to stimulus from interferon-gamma (IFN-γ and proinflammatory cytokines, MSCs also secrete chemokines and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)[45]. This results in a close proximity of immune cells allowing the local immunosuppressive environment to have a more pronounced effect[49].

A substantial amount of work has been focused on the potential for MSCs to treat GVHD. Ringdén *et al*[50] treated 8 patients, who had developed steroid-refractory GVHD, with bone marrow derived MSCs. In 6 of these patients acute GVHD ameliorated. The same group later went on to perform a phase Ⅱ trial consisting of 55 patients with acute GVHD. In this trial, 30 patients completely recovered from GVHD and a further 9 showed improvement. None of the patients developed adverse reactions due to the administration of MSCs[51]. Another phase one trial administering MSCs for GVHD was carried out by Introna *et al*[52] This multicentre study looked at 40 patients (15 children and 25 adults) with steroid resistant GVHD and gave them a median of 3 third-party derived MSCs infusions. Here it was found that the MSCs had a 67.5% T cell mediated response rate with a 27.5% complete response, 86 adverse effects were reported however most of these were of an infectious nature (72.1%) and not due to the administration of MSCs[52]. They concluded that MSCs could safely be administered in addition to conventional immunosuppression (*e.g.*, cyclosporin, steroid). Despite these positive results, there is some concern over a phase III clinical trial that failed to meet its primary clinical end point (NCT00366145)[53]. In this trial, patients received 8 infusions of 2×10^6 cells/kg over 4 wk and 4 more infusions administered weekly after 28 d. The trial did not meet its primary end point of a significant increase of

complete response of steroid resistant GVHD. Galipeau *et al*[54] provides a comprehensive failure analysis of the trial. The main conclusion of this analysis is that there are significant differences between the Martin study and studies from Europe that could account for the failure, in particular the passage number of the cells used[54]. As such, this study is not damning of MSCs but rather provides more areas that require examination before they can be used more widely.

Unlike the other cell types, there are now completed early clinical trials that have deployed MSCs as a therapy for SOT. The largest comes from Tan *et al*[55] In their trial they had 159 kidney transplant patients split into 3 groups, with 2 groups receiving autologous MSCs with either standard dose calcineurin inhibitors (CNIs) or low dose CNIs and the control group receiving standard dose CNIs and anti-IL-2 receptor antibody. The major conclusions from this study were that the MSC groups had a lower incidence of glucocorticoid-resistant rejection, a faster recovery in renal function, and significantly decreased risk of opportunistic infections than the control group[55]. This study also addresses safety concerns over the use of MSCs as there were no adverse reactions reported in either of the test groups. However this trial was not without its problems. It was noted by the authors that the number of rejection episodes in the control group was higher than what would be expected. This made it appear that the MSC groups performed better than standard immunosuppression when this may not be the case[55]. Additionally, the major differences in graft function were only noticed in the first 2 wk. It is conceivable that this was due the regenerative abilities of MSCs repairing the reperfusion injury associated with all kidney transplants. And lastly, the major difference in opportunistic infections was noted in the MSC and low dose CNI group. As there was no control low dose CNI group, we cannot be certain that the observed reduction in infection is due to MSCs or simply due to the reduced use of immunosuppressive drugs.

In addition to the work from Tan there have been several case reports looking at the use of MSCs in a small number of SOT patients. Perico *et al*[56,57] have performed two pilot studies looking at the use of MSCs in kidney transplantation in 4 patients. In their first study they administered intravenous autologous MSCs 7 d after transplantation and followed the patients for 360 d. From days 7 to 14 post transplant, serum creatinine increased in 1 of their patients, however acute graft rejection was excluded *via* biopsy. They also noted an increase in patient Tregs and a decrease in T cell expansion post-transplant. Long term, both patients showed stable graft and the authors concluded that MSC infusion in kidney transplant recipients is feasible, allows increase of Treg in the peripheral blood, and controls memory $CD8^+$ T cell function[57]. In their second trial, they dosed two living-related kidney transplant recipients with autologous MSCs one day before transplantation. The change in dosing time was an attempt to avoid the acute graft deterioration observed to be caused by intragraft localization of MSCs when dosing 7 d post-transplant. Although both patients had no side effects to the MSC infusion and both had stable graft function at 12 mo, one of their patients did have an acute rejection episode 14 d post-transplant that was resolved with corticosteroid therapy[57]. The authors attribute the rejection episode to a higher number of HLA mismatches. They concluded that pre-transplant administration of MSCs avoided the cell induced graft dysfunction associated with post-transplant MSC administration and that this method is favourable for future trials. Peng *et al*[58] examined the effect of autologous MSCs on renal transplants by giving 6 patients MSCs combined with half doses of tacrolimus and comparing acute rejection, graft function, and graft survival at 12 mo to a control group of 6 patients receiving standard dose tacrolimus. The results of this showed no toxic adverse effects associated with MSC infusion and all patients survived with stable graft function to 12 mo with only 1 acute rejection episode in the control group. The one difference they did notice was elevated B-cell counts in the MSC group at 3 mo compared to the control[58]. They concluded that MSCs may provide benefits in renal transplantation by reducing the required dose of conventional immunosuppressive drug that is required for long term graft survival. The results of these case reports are consistent with those of the Tan study, with no adverse reactions, stable graft function, reduced rejection, and the ability to lower maintenance immunosuppression (Table 1).

From these early clinical trials, summarised in Table 1, it is evident that MSCs have an acceptable safety profile and have beneficial effects for transplantation. There still remain several very important questions to be answered before MSCs can obtain mainstream clinical use. The issue of whether autologous or allogeneic MSCs are better is significant, with arguments for both being put forward. Tan *et al*[55] employed autologous MSCs because of the issues surrounding MSC isolation from deceased donors. Furthermore, the use of autologous MSCs would avoid any potential for rejection of the cells and a subsequent loss of their function. However, there is some evidence that MSCs are immuno-evasive allowing them to escape recognition by the hosts immune system[59]. If this is the case then allogeneic MSCs are promising as obtaining them will not impact the eventual recipient who may have serious health issues that could be exacerbated by the collection of MSCs or could impact the quality of the MSCs. The immuno-evasive status of MSCs also opens up the potential for third party derived MSCs. This would invalidate concerns about obtaining MSCs in the cases of deceased donors. Nevertheless, issues pertaining to the immunogenicity of allogeneic or third-party derived MSCs has not been substantially addressed *in vivo* and have not been addressed in large animal models. There are preclinical studies demonstrating that allogeneic MSC monotherapy alone failed to prevent allograft rejection[60-69]. Studies reporting on the benefits of allogeneic MSCs have also shown short term prolongation of graft

Table 1 Summary of clinical trials using mesenchymal stem cells in kidney transplantation

Ref.	Patient number	Cell number	Cell source	Adverse reactions	Graft survival
Tan *et al*[55], 2012	106	1-2 × 10^6 cells/kg	Autologous, bone marrow	None	100% at 1 yr
Perico *et al*[56], 2011	2	2 × 10^6 cells/kg	Autologous, bone marrow	Acute graft dysfunction	100% at 360 d
Perico *et al*[57], 2013	2	2 × 10^6 cells/kg	Autologous, bone marrow	HLA induced rejection	100% at 1 yr
Peng *et al*[58], 2013	6	5 × 10^6 1st dose 2 × 10^6 cells/kg 2nd dose	Donor derived, bone marrow	None	100% at 1 yr

HLA: Human leukocyte antigen.

survival[64]. More importantly, in some studies, pre-transplant allogeneic MSC monotherapy accelerated allograft rejection thereby questioning the immunoprivileged status of MSC. There is evidence that allogeneic MSCs can trigger an anti-donor immune response resulting in accelerated allograft rejection[65-67]. The co-administration of allogeneic MSC with immunosuppressive drugs however showed better outcome of the allograft compared to MSC monotherapy[63,64,70-72]. Therefore, the synergistic effects of allogeneic MSC with immunosuppressive drugs need to be taken into consideration in MSC therapy. We have previously reviewed in detail the mechanisms associated with allogeneic or third-party derived MSC immunogenicity and the synergistic effects of MSC with immunosuppressive drugs, in Sivanathan *et al*[43]. Questions around the dose rate, the timing, the route of administration, what happens to the cells and what exactly the MSCs are doing and their mechanism of action still remain unanswered. Given the state of the field it is not possible to accurately speculate on the answers to these questions. Additionally there is the potential for the modification of MSCs that further expands the possible methods of application

MODIFYING MSC FOR ENHANCED IMMUNOSUPPRESSION

The *ex vivo* manipulation of MSCs with proinflammatory cytokines, particularly IFN-γ modification of MSC enhances the immunomodulatory, reparative and homing potential of MSCs[43]. The enhancement of these MSC properties would be beneficial in a transplant setting and may hasten the translation of MSC therapy into SOT patients.

Of key benefit, the priming of MSCs with IFN-γ is critical to active MSCs immunosuppressive function[73-75]. IFN-γ primed MSC have an enhanced ability to suppress T cell responses compared to untreated MSC[76-80]. Increase suppression of T cell responses is mediated by the induction of immunosuppressive factors such as iNOS andIDO[75,81]. IDO is also well known for its roles in preventing rejection and induction tolerance at the fetal-maternal interface[82]. In addition, MSC-expressed IDO have been shown to induce tolerogenic DCs and Tregs[83], which are two other cell based therapies that have gained significant interest in SOT, as we have discussed above. The upregulation of other MSC immunomodulatory factors, the enhancement of negative T cell signalling, the inhibition of proinflammatory T cell response and the increase in Tregs further support the benefits of administering IFN-γ primed MSC therapy for SOT.

Regardless of the potential therapeutic benefits of IFN-γ primed MSC therapy, it should be noted that IFN-γ upregulate MHC class I and induces MHC class II expression on MSCs[84-86]. This may render these cells more immunogenic in MHC-mismatched recipients[43], thereby decreasing their effectiveness at suppressing inflammation as reported in some studies[87,88]. Only two studies have directly addressed IFN-γ primed MSC immunogenicity *in vivo*[88,89] and this warrants further investigation. Thus, when considering IFN-γ primed MSC therapy, then administration of autologous MSC may be more beneficial. If allogeneic or third-party IFN-γ primed MSC were to be considered, the co-administration of these cells with immunosuppressive drugs would be necessary as an attempt to control anti-donor immune response towards MSC to enable MSCs to exert their beneficiary effects *in vivo*.

CONCLUSION

In summary, there are numerous cell based therapies that have shown potential for use in the immunomodulation of SOT in pre-clinical, small, and large animal models. Tregs and DCs have shown promise *in vitro* and in animal models as well as displaying safety and efficacy in clinical trials involving GVHD, diabetes, and rheumatoid arthritis. However, only MSCs have completed large clinical trials to date. MSC have shown the most promise having been tested in GVHD and in early clinical trials for kidney transplantation. Based on the GVHD experience and the early transplant work, it appears that MSC have an acceptable safety profile and potential therapeutic effect. However, much needs to be resolved, including the issue of autologous *vs* allogeneic (third party cells), frequency of administration and mechanism of action. The optimal immunosuppressive therapy to be co-administered should also be studied. The results from these early trials are positive but have presented numerous issues that need to be addressed before MSCs gain widespread clinical use.

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