



Use of mesenchymal stem cells for chronic kidney disease

Byung Ha Chung^{ID}

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Despite advances in management of chronic kidney disease (CKD) with medications and renal replacement therapy, CKD remains a significant health issue. The regenerative ability of the kidney is limited, and usually inefficient to prevent progression of fibrosis. Unfortunately, currently available pharmacologic agents cannot halt tissue injury in CKD. So, CKD may finally progress toward end-stage renal disease, and morbidity and mortality of patients with CKD remains high [1]. Much effort to identify novel therapies, to retard kidney damage in CKD, has been made. Of such efforts, mesenchymal stem cells (MSCs) are of interest, because of their potential therapeutic effects, regarding kidney disease from a few years ago. The effectiveness of MSCs in treatment of kidney disease, has been extensively investigated in pre-clinical models, and systemic review of data, suggested that results are promising [2]. Therapeutic potential of MSCs is mediated by multiple mechanisms, such as immunomodulatory effects through secretion of regulatory cytokines, activation of regulatory immune cells, and the capacity to increase cellular repair through secretion of anti-apoptotic, anti-fibrotic, and up-regulation of renal developmental markers as well [3] (Fig. 1). These mul-

iple functions of MSCs, supposedly lead to multifaceted strategies in various models of kidney disease.

In the issue of *Kidney Research and Clinical Practice*, Villanueva et al [4] assessed the efficacy and safety of an injection, of autologous adipose tissue-derived MSCs (AT-MSCs), for treatment of CKD. They infused AT-MSCs intravenously into 6 patients with CKD, at a dose of 1×10^6 /kg. This dose was the most frequently used in previous studies, and proved not to be associated, with adverse events as well [5]. Estimated glomerular filtration rate (eGFR), assessed by the Modification of Diet in Kidney Disease, formula was 20–40 mL/min/1.73 m². The cause of CKD was different in each patient; 1) focal and segmental glomerulosclerosis, 2) immunoglobulin A nephropathy, 3) post-acute kidney injury RIFLE stage L, 4) tubulointerstitial chronic nephritis due to Sjögren's disease, 5) renal dysplasia, and 6) hypertensive glomerulosclerosis. All patients were medicated, including administering of renin-angiotensin blockade, before enrollment and during the study. As a result, no adverse effect was detected in all patients, and eGFR did not decrease significantly after AT-MSCs infusion, during the follow-up period of 1 year. Of note, significant improvements in urinary protein excretion were detected in some patients. So, despite limitations of this study, especially because of the small number of included patients without control groups, they suggested that AT-MSCs infusion was not associated with adverse effects, and may benefit patients already undergoing standard medical treatment for CKD.

There have been few clinical trials, which investigate the safety and therapeutic potential of MSCs, in patients with various types of CKD [6]. Most of the trials have been phase I or II studies, and had limitations in number of patients, and study design as well (Table 1). Considering complex processes and expensive infrastructures required to produce qualified MSCs, it is difficult to per-

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Correspondence: Byung Ha Chung

Department of Internal Medicine, Seoul St. Mary's Hospital, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea. E-mail: chungbh@catholic.ac.kr

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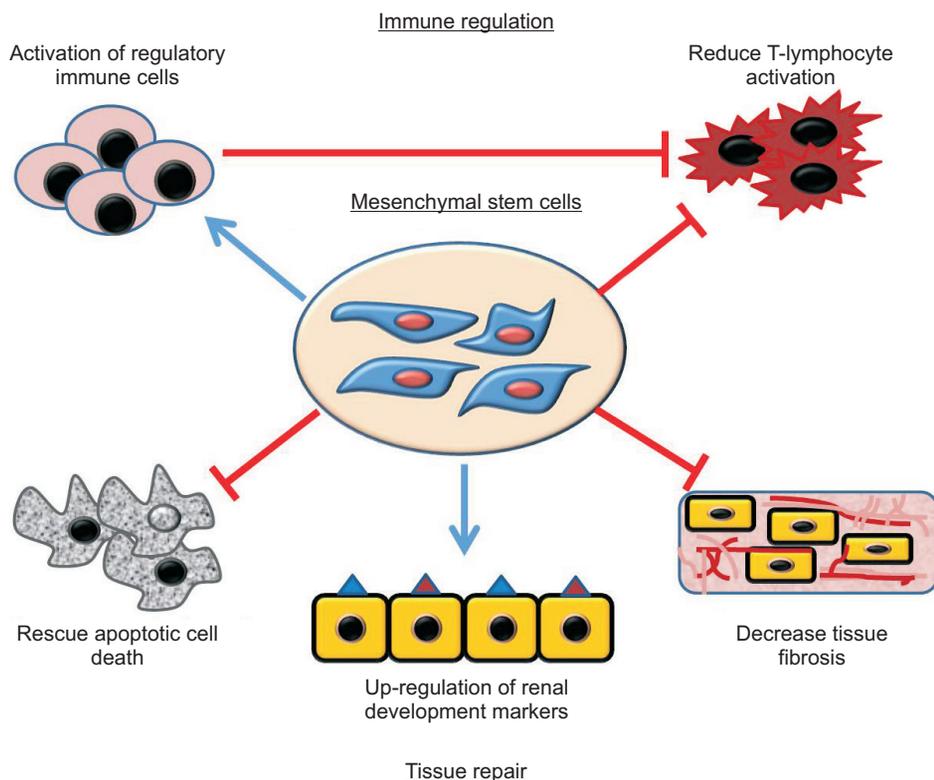


Figure 1. Proposed action mechanisms of mesenchymal stem cells in the treatment of chronic kidney disease.

Table 1. Clinical trials of mesenchymal stem cells application in chronic kidney disease (<https://ClinicalTrials.gov>)

ClinicalTrials.gov Identifier	Study title	Conditions	Interventions	Phase/study design
NCT02195323	Autologous bone marrow derived-MSCs in patients with CKD	CKD	Intravenous injection of MSCs	Phase 1/open label, single group assignment
NCT03321942	Treatment of chronic renal failure with adipose tissue-derived MSCs	CKD/renal interstitial fibrosis	MSCs treatment (treatment group) vs. conventional treatment (control group)	Not applicable/open label, randomized
NCT02166489	MSCs transplantation in patients with chronic renal failure due to polycystic kidney disease	CKD due to polycystic kidney disease	Intravenous injection autologous MSCs	Phase 1/open label, single group assignment
NCT02966717	Rituximab combined with MSCs in the treatment of primary nephrotic syndrome (3–4 Stage of CKD)	Renal insufficiency/ chronic nephrotic syndrome	Conventional therapy vs. rituximab & MSCs	Phase 2/open label, randomized
NCT02266394	Hypoxia and inflammatory injury in human renovascular hypertension	Renal artery stenosis/ CKD	MSCs delivery with stent placement	Phase 1/open label, non-randomized
NCT00659620	MSCs transplantation in the treatment of chronic allograft nephropathy	Kidney transplant/ chronic allograft nephropathy	Intravenous injection of MSCs	Phase 1, 2/open label, single group assignment
NCT01840540	MSCs for occlusive disease of the kidney	Atherosclerotic renal artery stenosis	Arterial infusion of autologous MSCs	Phase 1/open label, single group assignment
NCT03840343	Patient-derived stem cell therapy for diabetic kidney disease	Diabetic kidney disease	Autologous adipose-derived MSCs: lower dose vs. higher dose	Phase 1/open label, non-randomized

CKD, chronic kidney disease; MSCs, mesenchymal stem cells.

form large scale, well-designed clinical trials. Many trials, including this study [4], consistently indicated that MSCs may have potential, as a new therapeutic strategy, in combination with standard pharmacologic therapies. There are many issues which should be resolved for MSCs, to become a widely accepted treatment option for CKD patients. First, optimal dose and infusion method of MSCs should be established. Unlike in animal models, a non-invasive infusion method should be considered in humans. That's why peripheral intravenous injection was most frequently used in previous clinical trials. However, in this situation, a significant portion of infused MSCs can be removed in the lung or spleen, during their circulation within the body. So, if low doses of MSCs were infused, we cannot expect an adequate therapeutic effect, because only a small number of MSCs can reach kidneys. Meanwhile, a high dose of MSCs can be associated, with severe adverse events, as mentioned in the article [7]. In this regard, optimal range of cell number according to infusion method should be determined. Second, to maintain therapeutic potential of MSCs after infusion is also a significant issue. The effectiveness of MSCs can decrease after injection, because of poor micro-environments such as low oxygen, inflammatory condition, and free radicals [8]. So, to improve the quality of MSCs before treatment would be an innovative strategy in MSCs-based therapy. Cultivation of MSCs under hypoxic condition or bioactive molecules, and use of MSCs conditioned-medium or MSCs derived micro-vesicles have been proposed to increase effectiveness of MSCs in pre-clinical study. Those results should be evaluated, in clinical studies in the future [9]. Third, the source of MSCs must be discussed. There are three available sources for MSCs generation; adipose tissue, umbilical cord blood cells, and bone marrow. The effectiveness of MSCs may not differ, according to type of source. However, when adipose tissue or bone marrow were used as a source of MSCs, 'autologous' and 'allogeneic' MSCs can be generated. Autologous MSCs have some advantages, because patient's tissue derivatives can be more compatible to patients themselves. Additionally, autologous MSCs can escape from rejection or cell damages induced by allo-immune system of the host, which may occur when allogeneic MSCs are used [9]. However, to generate autologous MSCs in each patient require an expensive and time-consuming process. Additionally, the quality of MSCs can be different in each

individual. For example, a patient with diabetic nephropathy was excluded from the study, because of poor proliferation, and resulting low number of AT-MSCs in culture, in this study [4]. So, for mass-production of standardized "cell therapy agent", allogeneic MSCs can be preferred. But to improve therapeutic potential, and to decrease the possibility of rejection, are remaining problems to resolve. A recent report suggested that human-induced pluripotent stem cells (iPSCs)-derived MSCs can be used as an active cell resource for regenerative medicine. The iPSC-MSC is expected to enable personalized medicine, by an unlimited number of homogenous autologous MSCs in each patient [10].

In summary, theoretically, MSCs can possibly halt and retard progression of tissue damage in CKD, and has been extensively investigated in pre-clinical studies. If those beneficial effects can be evaluated in large scale clinical trials, as well as optimal cell dose and injection method, the source of MSCs can be standardized, MSCs will be accepted as innovative therapy for regenerative treatment of CKD.

Conflicts of interest

The author has no conflicts of interest to declare.

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