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Bone marrow–mesenchymal stromal cell infusion in patients with chronic kidney disease: A safety study with 18 months of follow-up

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Abstract

Background. Chronic kidney disease (CKD) is a progressive loss of kidney function and structure that affects approximately 13% of the population worldwide. A recent meta-analysis revealed that cell-based therapies improve impaired renal function and structure in preclinical models of CKD. We assessed the safety and tolerability of bone marrow–mesenchymal stromal cell (MSC) infusion in patients with CKD. *Methods.* A single-arm study was carried out at one center with 18-month follow-up in seven eligible patients with CKD due to different etiologies such as hypertension, nephrotic syndrome (NS) and unknown etiology. We administered an intravenous infusion ($1–2 \times 10^6$ cells/kg) of autologous cultured MSCs. The primary endpoint was safety, which was measured by number and severity of adverse events. The secondary endpoint was decrease in the rate of decrease in estimated glomerular filtration rate (eGFR). We compared kidney function during the follow-up visits to baseline and 18 months prior to the intervention. *Results.* Follow-up visits of all seven patients were completed; however, we have not observed any cell-related adverse events during the trial. Changes in eGFR ($P = 0.10$) and serum creatinine ($P = 0.24$) from 18 months before cell infusion to baseline in comparison with baseline to 18 months were not statistically significant. *Conclusions.* We showed safety and tolerability of a single-dose infusion of autologous MSCs in patients with CKD.

Key Words: *cell therapy, chronic kidney diseases, clinical trial, mesenchymal stromal*

Introduction

Chronic kidney disease (CKD) is defined as a progressive loss of kidney function and structure over time that affects 11.7–15.1% of the world population [1]. Ageing, hypertension and diabetes are the most common causes of CKD [2,3]. Despite advances in management of CKD by using medications and renal replacement therapies, CKD still remains an important public health issue due to its various complications and huge disease burden.

Patients with final stages of CKD share a common appearance of glomerulosclerosis, vascular sclerosis and tubulointerstitial fibrosis, regardless of underlying disease [4–7]. The appearance that suggests a common final pathway of progressive injury, which is associated with apoptosis, oxidative damage and microvascular rarefaction [8], mesengial and fibroblast activation, renin–angiotensin–aldosterone system (RAAS) activation, various cytokines and growth factors production, epithelial-mesenchymal transition (EMT), and monocytes, macrophages and T-cell infiltration [4,5,9,10]. These pathways can be attenuated.

Actually, the kidney has regenerative capacity, which leads to organ recovery [11]. Unfortunately, this ability is limited and usually inefficient to prevent fibrosis [12].

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Importantly, CKD may finally progress toward end-stage renal disease (ESRD). Therefore, novel therapies to stop or retard the kidney damage process are required.

Following promising results of stem cell transplantation in CKD models in recent decades, this method is taken into consideration in pre-clinical and clinical setting. Mesenchymal stromal cells (MSCs) are undifferentiated adult stem cells of mesodermal origin that were originally identified in the bone marrow (BM) stroma by Friedenstein *et al.* [13]. They are plastic-adherent cells that express CD105, CD73 and CD90, and lack CD45, CD34, CD14 or CD11b, CD79 alpha or CD19 and HLA-DR surface molecules. Also, these cells are able to differentiate to osteoblasts, adipocytes and chondroblasts *in vitro* [14]. They are renoprotective cells that act mainly in a paracrine manner by releasing some proteins and hormones, transferring extracellular vesicles and mitochondria through tunneling nanotubes or microvesicles [15], which eventually impact on apoptosis, fibrosis, inflammation and microvascular rarefaction that make them a proper option for treating CKD [16–19].

A systematic review and meta-analysis revealed that cell-based therapies, mostly MSCs, improved impaired renal function and structure in preclinical models of CKD [20]. Previously we reported that gentamicin nephrotoxicity could be ameliorated by human MSC–conditioned medium (MSC-CM) [21]. Furthermore, we stated that intrarenal arterial infusion of BM-MSCs improved renal function and structure in an acute kidney injury (AKI) model [22] and a CKD model of rhesus *Macaca mulatta* monkey [23].

Moreover, an Egyptian group showed that infusion of MSCs in patients with CKD was promising; however, they did not report and discuss any safety issues [24,25]. Both their trials had short-term follow-up periods (3 and 6 months) and they recruited a limited number of CKD patients with heterogeneous etiologies. Packham *et al.* reported that allogeneic BM-derived mesenchymal precursor cells (MPCs) were safe in patients with diabetic nephropathy (DN) [26], but the safety of an autologous source of MSCs in other types of CKD has been still an issue that is addressed by this article. Recently, we showed the safety of MSCs in autosomal dominant polycystic kidney disease patients [27]. Here, we tried to evaluate safety and tolerability of autologous MSCs in nondiabetic CKD patients with long-term follow-up evaluation.

Materials and methods

Study design and enrollment criteria

The study was an open-label, single-arm trial in a single center that was designed to evaluate safety and tolerability of an autologous MSC infusion in CKD patients.

Inclusion criteria were as follows: male or female patients; presence of CKD confirmed with serum and urine analysis; a glomerular filtration rate (GFR) of 25–60 mL/min/1.73 m^2; age between 25 and 60 years old and ability to understand and willingness to sign consent form. Exclusion criteria were as follows: being pregnant or lactating; underlying diseases such as diabetes and malignancy; having hematologic or liver diseases; having a past history of chronic transplant rejection; being unable to follow postoperative exercise regimen or return for evaluations. All subjects had a medical file at the clinic for at least 18 months prior to enrollment. We recommended the participants continue medication and follow a low-salt and low-protein diet during the study. All patients gave their written informed consent prior to enrollment.

We conducted the study in accordance with current International Conference on Harmonisation—Good clinical practice (ICH-GCP) guidelines and the Declaration of Helsinki. The Ethics Committee of Royan Institute and the Institutional Review Board (IRB) approved this study. A trial monitor and Data Safety Monitoring Board (DSMB) observed the whole trial to ensure the safety of participants. The trial schedule is shown in Figure 1. The trial was registered on www.ClinicalTrials.gov (NCT02195323).

Primary endpoint: safety and tolerability

Primary endpoint was the safety issue so the number, type and grade of adverse events (AE) and serious adverse events (SAE) related to cell infusion were assessed throughout the study according to common terminology criteria for adverse events (CTCAE) version 4.0. We also evaluated clinical parameters (physical examination and blood pressure changes) and paraclinical changes (complete blood count [CBC], fasting blood sugar [FBS], hemoglobin A1c [HbA1c], serum electrolytes, serum albumin, blood lipid profile, uric acid, liver function tests, erythrocyte sedimentation rate [ESR], parathyroid hormone [PTH], thyroid-stimulating hormone [TSH], dipstick proteinuria and urine culture).

Secondary endpoint

The secondary endpoint was decrease in the rate of decrease in estimated glomerular filtration rate (eGFR), which was evaluated by comparing eGFR decrease between two 18-month periods before and after cell infusion (baseline to 18 months after cell infusion versus 18 months before the infusion to baseline). The eGFR was calculated usingy the Modification of Diet in Renal Disease (MDRD) formula and diethylenetriamine pentaacetate (DTPA) scan. We also