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Intraarterial Autologous Mesenchymal Stem Cell Therapy for Diabetic Kidney Disease

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INTRODUCTION

Diabetic kidney disease (DKD) is characterized by vascular damage because of chronic sterile inflammation, increased oxidative stress, accumulation of advanced glycation end-products, steatosis, insulin resistance, kidney hypoxia, cellular senescence abundance, and altered renin-angiotensin-aldosterone system activation. Sodium-glucose cotransporter inhibitors, glucagon-like peptide-1 receptor agonists, nonsteroidal mineralocorticoid receptor antagonists, and endothelin A receptor antagonists have reduced cardiovascular morbidity and mitigated loss of kidney function in DKD.[1] However, inflammation remains a key pathological mechanism not fully addressed. Therefore, there is a need for development and optimization of multitargeted therapeutic approaches to effectively address complex pathogenesis underlying progressive DKD.[2]

Mesenchymal stem/stromal cells (MSCs) are adult stem cells isolated from various sources (e.g., bone marrow, fat, and umbilical cord) which facilitate tissue repair through the release of growth factors, cytokines, chemokines, and extracellular vesicles and through cell-cell interactions. In experimental DKD models, MSCs reduce glomerulosclerosis, microalbuminuria, inflammation, oxidative stress, and fibrosis.[3] In December 2024, a major milestone was reached with the US Food and Drug Administration approval of the first MSC therapy (Ryoncil) for pediatric steroid-refractory acute graft-versus-host disease.[4] This US approval, along with those in other countries, underscores MSC therapeutic potential and highlights the need for DKD investigations. Based on our previous investigations in patients with atherosclerotic renovascular disease,[5,6] we hypothesized that administration of autologous, adipose tissue–derived MSC with intraarterial delivery via the renal artery in patients with DKD would be both feasible and safe. This single-center, open-label, dose-escalating trial was conducted at Mayo Clinic (Rochester, MN) to evaluate the safety (phase 1), tolerability, and dose response of intraarterial delivery of autologous adipose-derived MSC in participants with progressive DKD.

RESULTS

Screening and Enrollment

From 2019 to 2020, after detailed assessments, only 2 individuals were invited for formal screening and were enrolled (Supplementary Table S1 and Supplementary Figure S1). After adipose tissue collection, MSC were

harvested, expanded, and cryopreserved for administration. Study participant(s) received 2 MSC infusions of 2.5×10^5 cells/kg at time 0 and 3 months, as shown in study schematic (Figure 1). One participant withdrew after declining intraarterial MSC administration. The second participant received MSC infusions on day 0 and month 4 (delayed by 1 month) because of care disruptions during the onset of the COVID-19 pandemic. Given public health restrictions on nonessential travel, further enrollment was halted, and trial follow-up was abbreviated. Subsequent nephrology care was managed locally.

Baseline Characteristics

The participant (White male aged > 70 years) had chronic kidney disease attributed to DKD and a 15-year history of diabetes, which was well-controlled (hemoglobin A1c: 6.9%) on insulin, metformin, and a glucagon-like peptide-1 receptor agonist. Hypertension was treated with a dihydropyridine calcium channel blocker, an angiotensin-converting enzyme inhibitor, and a thiazide diuretic. Proteinuria was < 100 mg/24 h. Baseline and periprocedural clinical laboratory values and safety assessments are detailed in Supplementary Table S2.

Safety and Tolerability

No infusion-related or MSC-related serious adverse events or procedural complications occurred. Serum creatinine transiently increased after MSC infusion(s) which included small volume iodinated contrast administration for limited vessel visualization (Supplementary Figure S2). Notably, the day 1 change in serum creatinine may have been influenced by recent i.v. contrast exposure from an unplanned clinical computed tomography cardiac imaging study performed 24 to 48 hours before MSC infusion. No significant changes were observed in erythrocyte sedimentation rate and C-reactive protein following treatment. However, leukocytes, platelets, and lactate dehydrogenase levels trended lower.

Kidney Function Change

The estimated (standard errors) annualized absolute change in estimated glomerular filtration rate (eGFR) in the period preceding MSC initiation was −7.02 (3.15) ml/min per 1.73 m^2/yr, compared with an estimate of −1.84 (0.53) ml/min per 1.73 m^2/yr in the post-MSC initiation period. eGFR values superimposed with the estimated annualized absolute change in eGFR in both pre- and post-MSC (approximately 5 years) periods are shown in Figure 2, with creatinine trajectories in Supplementary Figure S3.

DISCUSSION

This study demonstrates several novel and clinically relevant findings. To the best of our knowledge, this is the first clinical study to establish intraarterial renal delivery of autologous MSCs in DKD. MSC manufacturing of therapeutically viable autologous MSC was feasible, even when derived from an older individual with DKD. Intraarterial administration was

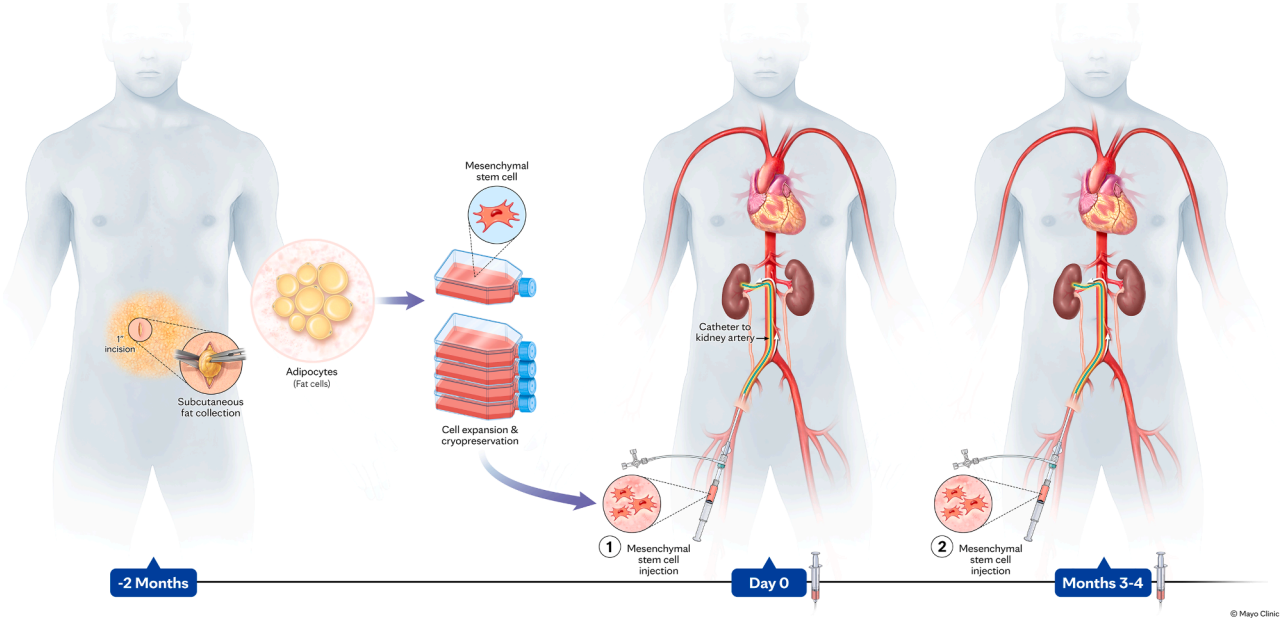

Figure 1. Study schematic. Clinical trial study flow included subcutaneous harvest of adipose tissue through a 1- to 2-inch incision in the periumbilical region of the abdomen. Adipose tissue was digested for isolation, harvest, and expansion of MSCs, which later underwent rigorous testing, and then cryopreservation until use. MSCs were administered via the renal artery (same kidney) approximately 3 to 4 months apart. Figure used with permission of Mayo Foundation for Medical Education and Research, all rights reserved. MSC, mesenchymal stem cell.

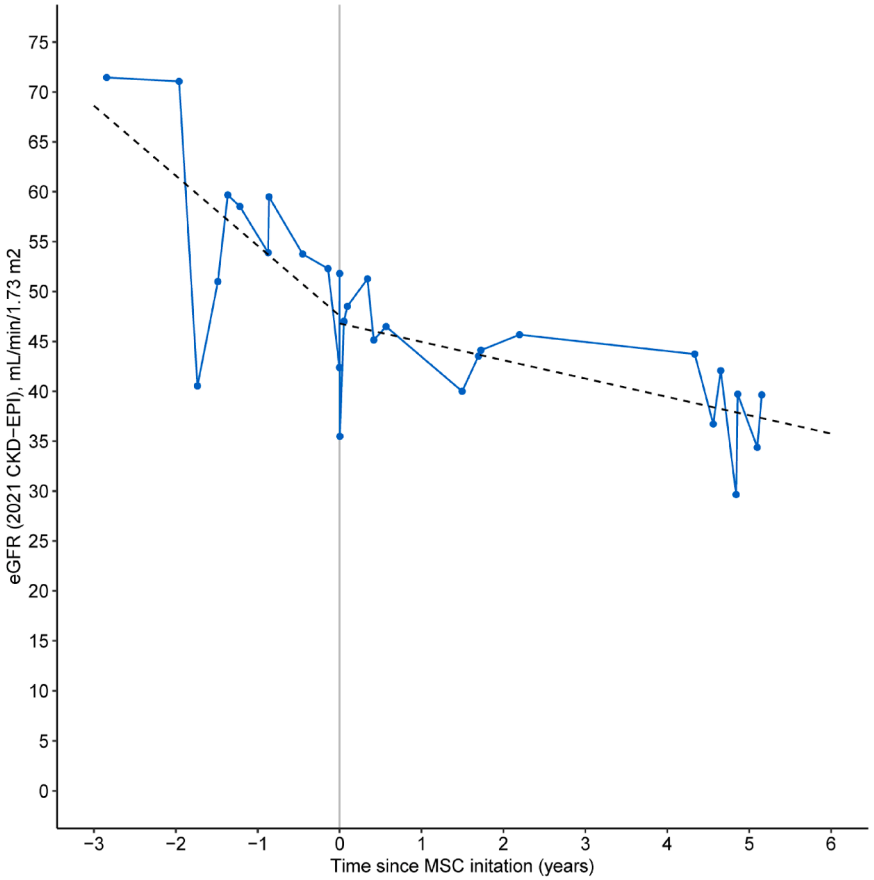

Figure 2. Long-term kidney function follow-up: before and after MSC therapy. Changes in kidney function (using the 2021 CKD-EPI eGFR) before and after MSC infusion. CKD-EPI, Chronic Kidney Disease–Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MSC, mesenchymal stem cells.

well-tolerated. Notably, MSC therapy was associated with marked attenuation of kidney function decline (−7.0 to −1.8 ml/min per 1.73 m^2/yr). Recently, the US Food and Drug Administration recognized eGFR slope as an acceptable surrogate end point for accelerated approval of rilparencel, a proprietary autologous cellular therapy, in the phase 3 REGEN-006 (PROACT 1) clinical trial for DKD.[7] Collectively, these findings support further investigation of MSC-based therapies as a potential strategy to delay DKD progression.

MSC Safety

In 2016, Packham *et al.*[8] conducted a multicenter, randomized, double-blind, dose-escalating, placebo-controlled trial evaluating i.v. administered allogeneic mesenchymal precursor cells in DKD participants ($n = 30$). No infusion-related or treatment-related serious adverse event was observed. In 2023, Perico *et al.*[9] reported findings from a multicenter, European trial applying bone marrow–derived, anti-CD362–selected allogeneic MSCs (ORBCEL-M) in adults with progressive DKD. Those randomized (3:1) to ORBCEL-M ($n = 12$) had safety determined and reduced function decline vs. placebo ($n = 4$). Consistent with these studies, our investigation demonstrated a favorable safety profile. However, the observed postprocedural rise in creatinine highlights the need to consider alternative arterial imaging strategies (e.g., CO_2) that avoid even minimal iodinated contrast agent exposure.

MSC Delivery Route

Local and intraarterial MSC delivery may enhance engraftment by circumventing the first-pass pulmonary effect and minimizing MSC sequestration in the lungs, as seen with i.v. delivery. Nonetheless, pulmonary macrophage-mediated efferocytosis following i.v. delivery may contribute to sustained proreparative signaling. Although i.v. is a less invasive and more cost-effective approach, intraarterial renal delivery has therapeutic promise. Abumoawad *et al.*[5] demonstrated improvements in kidney function and oxygenation in patients with renovascular disease receiving intra-arterial MSC (twice). Recently, Carstens *et al.*[S5] reported safety in intraarterial kidney delivery of autologous adipose–derived stromal vascular fraction cells in

patients with chronic kidney disease of unknown cause (Mesoamerican nephropathy; $n = 18$), with kidney function benefits identified in those with eGFR ≥ 30 ml/min per 1.73 m^2. Indeed, our patient with eGFR > 30 ml/min per 1.73 m^2 may have experienced long-term renal benefits following MSC therapy.

Combining MSC With Concomitant Glucose-Lowering Therapies for Optimal Kidney Repair Effects in Progressive Disease

In progressive DKD, it is essential to consider the influence of concomitant therapies such as angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, metformin, sodium-glucose cotransporter 2 inhibitor, glucagon-like peptide-1 receptor agonist, and nonsteroidal mineralocorticoid receptor antagonist. In the present case, an initial stabilization in kidney function was observed. However, subsequent episodes of acute kidney injury contributed to a continued, albeit slower, decline in eGFR. During long-term follow up, sodium-glucose cotransporter 2 inhibitor was initiated, likely between years 1.5 and 2.5. Of note, the participant exhibited progressive DKD despite longstanding glucagon-like peptide-1 receptor agonist and metformin, both which preceded MSC administration. These findings underscore the potential value of combining MSC therapy with contemporary antidiabetes agents to enhance therapeutic efficacy and reduce the cost burden of DKD care.[1,2]

CONCLUSION

Autologous MSC therapy delivered via intraarterial renal infusion was well-tolerated in our older participant with progressive DKD. When given alongside contemporary DKD therapies, MSC treatment was associated with significant slowing of DKD progression. This study represents a first of intraarterial MSC delivery in a patient with DKD and provides support for continued development of regenerative, cell-based strategies to halt kidney failure.

DISCLOSURE

LJH is a consultant for ETTA Biotechnology and Resolution Therapeutics. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

Data will be available for participant data that underlie the results reported in this article, after deidentification.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Consort diagram.

Figure S2. Early kidney function after MSC therapy.

Figure S3. Long-term kidney function (serum creatinine levels) before and after MSC therapy.

Table S1. Clinical trial inclusion and exclusion criteria.

Table S2. Periprocedural vitals, safety and clinical laboratory testing.

CONSORT checklist.

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