

## Case Report

# Case report: effect of umbilical cord mesenchymal stem cells on immunoglobulin A nephropathy after acute renal failure

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**Abstract:** Immunoglobulin A nephropathy is an inflammatory, autoimmune condition that may lead to renal impairment in its most aggressive forms. In this case report, a 50-year-old male with acute renal failure was diagnosed with IgA nephropathy, having elevated creatinine levels (3.0 mg/dL) and hypertension. He received intravenous infusions of a total of 120 million umbilical cord-derived mesenchymal stem cells (UC-MSCs) and was followed-up for 6 months. No adverse events were reported during or after administration or any of the follow-up visits. Creatinine levels decreased to and remained normal (1.0 mg/dL) in the 6 months following treatment. Anti-hypertensive medications were no longer needed. UC-MSC administration was safe, well-tolerated, and beneficial for this patient with IgA nephropathy.

**Keywords:** Mesenchymal stem cells, immunoglobulin A, IgA nephropathy, kidney failure, acute renal failure, umbilical cord, stem cells, creatinine

## Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is an autoimmune condition where IgA accumulates in the glomeruli of the kidney, resulting in chronic inflammation. While some cases may remain asymptomatic for years and are detected only post-mortem, IgAN may manifest in other patients with visible hematuria, hypertension or, in more severe cases, with a rapid loss in kidney function leading to renal failure [1]. The mucosal-mediated immune response following respiratory or gastrointestinal infections has been recognized as a possible trigger for IgAN episodes [1, 2]. During acute renal failure, the sudden loss of kidney function is associated with an increase in serum creatinine and electrolyte levels, as well as an increase in systemic inflammation due to inefficient management of waste and pathogens in the body [3, 4].

Mesenchymal stem cells (MSCs) are known to have anti-inflammatory, anti-apoptotic, and pro-angiogenic properties [5, 6]. MSC administration has been shown to be safe during the

past decade: a 2012 meta-analysis of over 1,000 subjects treated with intravenous MSCs revealed no toxicity or treatment-associated adverse events, with the exception of a mild fever experienced by a small group of subjects [7]. More recently, another meta-analysis aggregating over 2,500 subjects confirmed a similar safety profile [8]. MSCs have been proposed as an adjuvant therapy for kidney failure in preclinical, *in vitro*, and clinical studies [9-14]. More interestingly, umbilical cord MSCs have been observed to offer restorative and protective effects in a mouse model of IgAN [15], MSCs derived from human umbilical cord (hUC-MSC) have a greater capacity for proliferative expansion and enhanced therapeutic activity compared to MSCs derived from other sources, as well as a superior production of growth factors that stimulate secretions responsible for therapeutic potential [16-19].

This case report describes the administration of intravenous hUC-MSC in a patient diagnosed with IgA nephropathy after acute kidney failure, to confirm the safety of this therapeutic inter-

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**Table 1.** Hemoglobin, hematocrit, and blood pressure readings following UC-MSC administration

	Baseline	1 month	2 months	6 months
Hemoglobin (g/dL)	9.8	-	15.3	-
Hematocrit (%)	28.6	-	44.4	-
Blood pressure (mmHg)	160/90	130/80	-	120/89

vention as well as to investigate clinical improvement over a 6-month period.

### Case presentation

In December 2019, a 50-year-old male experienced lasting bilateral flank pain, malaise and diarrhea following an upper respiratory infection treated with azithromycin. He sought medical attention in January 2020 in the United States. Laboratory analyses revealed elevated creatinine levels (6.2 mg/dL), c-reactive Protein (74 mg/L), and potassium (6.4 mmol/L). The patient was admitted with high blood pressure. Further examination including renal biopsy revealed IgA nephropathy with low C3. The patient required several rounds of hemodialysis and treatment with cyclosporine, as well as treatment for pulmonary edema and hypertensive crisis. After stabilization, the patient was discharged with creatinine levels of 3.0 mg/dL.

In March 2020, the patient visited the Stem Cell Institute in Panama to be treated with human umbilical cord mesenchymal stem cells (hUC-MSCs). Informed consent was obtained prior to treatment. Upon physical examination, blood pressure was observed to be 160/90 mmHg (150/110 after repetition) with a pulse of 90 bpm. He was taking Adalat® (nifedipine) for his hypertension. His hemoglobin was 9.8 g/dL with 28.6% hematocrit (HCT), creatinine levels were 3.0 mg/dL, and blood urea nitrogen (BUN) levels were 26.0 mg/dL. The rest of the laboratory analyses and physical examination were unremarkable.

### Treatment

The patient was administered a total of 120 million hUC-MSCs intravenously over the course of 3 days, for which he provided written informed consent. Vital signs were measured immediately after administration and 30 minutes after administration. Adverse events, if any, were recorded. The patient was followed up after one month, two months, and six

months post-treatment. Changes in creatinine levels were visualized with a simple linear plot elaborated in GraphPad Prism 9.1.0 (216) for MacOS, GraphPad Software, LLC USA.

The hUC-MSCs used for this protocol were isolated from human umbilical cord tissue from voluntarily donated samples, negative for infectious diseases and following normal healthy births. The hUC-MSCs were processed according to current International Organization for Standardization (ISO) 9001 guidelines and Good Tissue Practices 21 CFR 1271 at MediStem Panama Inc. The cells were culture-expanded. Only cells meeting release criteria were used clinically as documented elsewhere [20]. In brief, release criteria for passage 5 cells were >75% viability and >95% positive for CD90, CD73, and CD105 cell surface markers as determined by flow cytometry, sterility, and negative for endotoxin (<2 EU/kg).

The dosage chosen for administration in the current trial was based on previous experience from our group utilizing hUC-MSC for intravenous therapy.

### Results

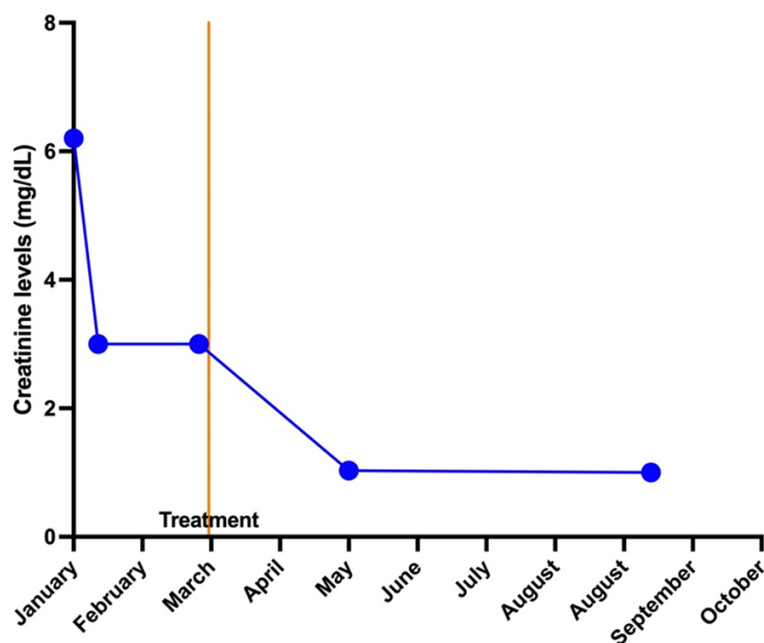
The infusion of hUC-MSCs were well-tolerated by the patient. No adverse events were reported during or after administration or any of the follow-up visits.

At the 1-month follow-up, the patient's blood pressure was down to 130/80 mmHg. He reported feeling "much better". At the 2-month follow-up, blood work revealed hemoglobin at 15.3 g/dL and 44.4% HCT (**Table 1**). His creatinine levels had decreased to 1.03 mg/dL (**Figure 1**). At the 6-month follow-up, the patient showed normal (120/80 mmHg) blood pressure readings. The creatinine levels remained at 1.0 mg/dL. The patient reported that he was no longer taking nifedipine due to improvement in blood pressure.

### Discussion

Although our patient was discharged after resolution of the acute crisis in January, creatinine levels remained elevated and unchanged (3.0 mg/mL) for two months following the episode,

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**Figure 1.** Creatinine levels (mg/dL) of acute renal failure patient. Renal failure occurred in Jan 2020. The patient received 120 million UC-MSCs in March 2020 and was followed up in May and September 2020.

and hypertension persisted despite nifedipine intake. This suggests that IgAN had not fully resolved by then. The patient experienced a marked and sustained amelioration in the months following hUC-MSC administration (**Table 1; Figure 1**). This amelioration was sustained during the six months of follow-up after hUC-MSC therapy. Additionally, at the time of this write-up, the patient was still in good health with no adverse events, albeit with some weight gain and high cholesterol 1.5 years after the last visit.

Most patients with acute renal failure (62%) return to baseline creatinine levels shortly after or in the following months after the hospital stay [21], but it may take as long as one year to return to normal renal function [22]. Those with non-resolving elevated creatinine levels are at a higher risk for long-term major adverse renal events [21]. In this case report, we observed (**Figure 1**) a noticeable drop in creatinine levels from elevated (3.0 mg/dL) to normal levels (1.03 mg/dL) two months after hUC-MSC administration. Hematocrit and hemoglobin levels also improved (**Table 1**). Nifedipine, the medication taken by the patient, has not been significantly associated with improved renal function or creatinine clearance [23-25].

Current therapeutic approaches for IgAN prioritize administration of corticosteroids and/or immunosuppressants to reduce circulating IgA, as well as antihypertensives to control blood pressure [26, 27]. Long-term treatment with low dose cyclosporin has some limited effects on proteinuria [28], but the patient of this case report was only treated with cyclosporin during his acute episode and not in the subsequent months. Since spontaneous IgAN remission has been observed after 3 years with conservative treatments such as dietary changes [29, 30], the possibility that this patient experienced an amelioration due to natural course of the disease cannot be ruled out.

However, considering that the patient's renal condition improved following hUC-MSC administration, the anti-inflammatory and auto-immune properties of MSCs could have restored the aberrant immune response that triggered the IgAN episode. The angiogenic and regenerative properties of MSCs could have also specifically targeted the damage to the kidney following renal failure. The mechanism of action to explain this improvement requires further investigation: insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) secreted by MSCs, as well as M2 activation, have been proposed as key factors for MSC renoprotective effects in preclinical models [12]. Similarly, the induction of T regulatory cells and the activation of the tumor growth factor beta (TGF- $\beta$ ) pathway were found to play a significant role in renal function amelioration in an animal model [14]. Modulation or inhibition of T-cell-dependent activation pathways to decrease the immune hyperresponsiveness (manifested in IgA overproduction) has also been considered as a possibility for IgAN therapy [2].

This is a single case report for this particular condition. A broader conclusion following these promising results would be premature at this

stage, especially given the variable prognosis of IgAN nephropathy. Indeed, IgAN has a complex, heterogeneous pathogenesis, with variability in patient proteinuria, hematuria, and histologic/immunohistochemical findings that should be considered when investigating new therapeutic possibilities [31].

We hope that this first, exploratory report will lead to further research in this field. Large, blinded, placebo-controlled, randomized trials are needed to determine the short and long-term effects of UC-MSC therapy following acute renal failure associated to IgA nephropathy, particularly to establish the mechanisms of the anti-inflammatory and trophic effects of MSCs in renal recovery.

### Acknowledgements

We thank the patient for his cooperation in the preparation of this case report; he provided written informed consent prior to treatment and consent for publication was also obtained. IRCM IRB supervised the de-identified medical record reviewing process.

### Disclosure of conflict of interest

None.

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