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See related article, "Opposing Roles of Dendritic Cell Subsets in Experimental GN," on pages 138–154.

## Mesenchymal Stromal Cells for AKI after Cardiac Surgery

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AKI is a common complication of cardiac surgery. Reported incidence ranges from 3.1% to 42%,<sup>1,2</sup> with the wide range reflecting differing definitions for cardiac surgery-associated AKI<sup>3</sup> and variation in patient baseline characteristics and surgery type.<sup>4</sup> Patients with AKI are burdened by high early perioperative and late mortality, prolonged hospitalization, and increased health care costs.<sup>5,6</sup> Among survivors, ARF is usually partially reversible, but many patients show incomplete recovery of renal function and are at an increased risk of late progression to CKD.<sup>7</sup> Factors thought to contribute to AKI after cardiac surgery include renal hypoperfusion, the activation of inflammatory and oxidative stress pathways, and exposure to nephrotoxic agents before and after the procedure.<sup>1</sup> Our understanding of the pathophysiology of renal injury remains rudimentary, and therapeutic options are elusive.

Numerous preclinical studies have explored cell-based technologies using mesenchymal stromal cells (MSCs),<sup>8</sup> with the goal being promotion of the regenerative capacity of the kidney. The administration of MSCs to rodents in experimental AKI has raised the prospect of a powerful treatment to repair acutely damaged kidneys, exploiting the unique MSC tropism for injured tissue and their paracrine anti-inflammatory and proregenerative properties.<sup>8,9</sup> The preclinical studies have provoked considerable interest in exploring the therapeutic potential of MSC-based therapy in AKI.

In this issue of the *Journal of the American Society of Nephrology*, Swaminathan *et al.*<sup>10</sup> provide the first full report on the use of MSCs in patients with postcardiac surgical AKI. In this rigorous phase 2, randomized, double-blind trial performed in 27 North American centers, patients experiencing AKI within 48 hours of cardiac surgery were given single intra-aortic administration of allogeneic MSCs ( $2 \times 10^6$  cells per kg body weight) or placebo. In addition to exploring safety, the trial was designed to evaluate, as the primary outcome, the

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efficacy of this cell therapy in reducing the time to recovery of kidney function after postoperative AKI. The study was terminated prematurely due to futility, because after 156 patients had been enrolled, time to renal function recovery, the need for dialysis, and 30-day all-cause mortality were not significantly different in the MSC- compared with placebo-treated group.

How should we view these negative and somewhat disappointing results? Is there still promise for MSCs as a treatment for postoperative AKI? The dose of MSCs used in this trial is similar to that used in other clinical settings, such as graft-versus-host disease or kidney transplantation. More than one half of the patients had impaired kidney function before cardiac surgery, although explorative subanalyses did not reveal any difference in the time to kidney function recovery between MSC- and placebo-treated patients with relatively preserved eGFR (eGFR  $\geq$  60 ml/min) compared with those with more reduced renal function. Patients with AKI were identified by a postoperative increase in serum creatinine  $>0.5$  mg/dl from baseline within 48 hours of removal from cardiopulmonary bypass. It is possible that earlier intervention might still show benefit given the inevitable delays in diagnosing AKI on the basis of a rise in serum creatinine<sup>11</sup>; perhaps in the future, other plasma and urinary biomarkers, such as kidney injury molecule-1, IL-18, neutrophil gelatinase-associated lipocalin, and matrix metalloproteinase-7, will improve the early detection of AKI.<sup>1,12–14</sup> It is also worth noting that the median cardiopulmonary bypass time was longer in the MSC than in the placebo group; prolonged cardiopulmonary bypass duration is associated with an increased risk of morbidity and mortality after cardiac surgery.<sup>15</sup> Nevertheless, these results are a setback for MSC therapy for established AKI.

A preliminary report of a phase 1 study with MSCs for prevention of AKI in patients undergoing cardiac surgery (clinicaltrials.gov; NCT 00733876) supports the hope that preventive interventions may still show promise.<sup>16,17</sup> In 16 patients undergoing on-pump cardiac surgery, who were at high risk for postoperative AKI due to underlying CKD, advanced age, diabetes mellitus, congestive heart failure, or chronic obstructive lung disease, bone marrow-derived MSCs were infused into the suprarenal aorta after completion of surgery. Compared with matched historical controls, MSCs seemed to protect early and late postsurgery kidney function against AKI development (0% versus 20% AKI incidence) and reduce the length of the hospital stay and the need for patient readmissions. These very preliminary results, although lacking a randomized control group, raise the possibility that, in the cardiac surgery setting, MSCs could be more effective for preventing than treating ongoing AKI.

While waiting for more robust studies testing the effectiveness of MSC treatment to prevent AKI in patients undergoing cardiac surgery, efforts should focus on improving prediction models for AKI after cardiac surgery, enabling identification of the subset of patients who could most benefit from effective

prevention.<sup>18–20</sup> The recently proposed prospective United Kingdom study in  $>30,000$  patients could contribute to this goal.<sup>21</sup> Given the anticipated high cost of MSC treatment, it will be important to anticipate the expected severity of AKI after cardiac surgery, and future studies may elect to limit enrolment to patients at high risk of severe AKI, avoiding the use of a costly intervention for those expected to recover spontaneously or with conventional therapies.

Notably, the trial did support the safety and tolerability of bone marrow-derived MSCs, with no evidence of severe injection reactions or long-term adverse events, including infections or the *de novo* development of malignancies. These results are consistent with the reassuring safety profile of MSCs from both academic and commercial manufacturers reported in kidney transplant recipients, patients with CKD, and patients with other conditions.<sup>22</sup> Nevertheless, data about the risk and degree of immunization after allogeneic MSC therapy are scarce in the literature and are not reported in this trial. Although MSCs are low-immunogenic and immune-evasive cells,<sup>23</sup> studies in patients treated with allogeneic MSCs should include long-term monitoring of anti-HLA antibody development to determine if there is any risk of immune sensitization, because sensitization could limit access to organ transplantation.

In summary, like most major clinical trials, this study gives us important new information but also leaves many unanswered questions about the renoprotective and reparative effect of MSC treatment in patients with AKI after cardiac surgery. It highlights the need for more research into the biologic mechanisms of actions of these cells, knowledge that will be crucial to informing the design of future large clinical trials of the therapeutic potential of MSCs.

## DISCLOSURES

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See related article, "Allogeneic Mesenchymal Stem Cells for Treatment of AKI after Cardiac Surgery," on pages 260–267.

## Clusters Not Classifications: Making Sense of Complement-Mediated Kidney Injury

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In 2010, we suggested the name C3 glomerulopathy to encompass a group of glomerular diseases characterized by the presence of glomerular C3 in the absence of substantial Ig and without deposition of the early components of the classic or lectin pathways of complement activation.<sup>1</sup> Within this new disease classification, two morphologic appearances could be recognized—dense deposit disease (DDD), first described in 1963,<sup>2</sup> with typical highly osmiophilic deposits on electron microscopy (EM), and C3GN, more recently recognized as a distinct entity,<sup>3</sup> showing isolated C3 without very dense deposits. The distinction between DDD and C3GN is not always straightforward, and there are patients with overlap cases on which not all pathologists would agree. By light microscopy, about 70% of patients with C3 glomerulopathy showed a membranoproliferative pattern, whereas the others showed mesangial proliferation.<sup>4</sup> Superimposed on these basic patterns were variable degrees of endocapillary hypercellularity, crescent formation, and glomerulosclerosis.

The implication of the finding of isolated glomerular C3 was that there was an inability to regulate activation of complement through the alternative pathway. We considered that identifying the factor(s) that caused this would help us to both understand the mechanism of renal injury and identify patients most likely to benefit from complement-inhibiting therapies.<sup>1</sup> This was our motivation for the classification. Mechanisms of alternative pathway dysregulation in C3 glomerulopathy include genetic and acquired factors. Genetic causes include deficiency of factor

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