

- Artyomov MN, Kurts C, Murphy KM, Miner JH, Shaw AS: Opposing roles of dendritic cell subsets in experimental glomerulonephritis. *J Am Soc Nephrol* 29: 138–154, 2018
6. Carlin LM, Stamatiades EG, Auffray C, Hanna RN, Glover L, Vizcay-Barrena G, Hedrick CC, Cook HT, Diebold S, Geissmann F: Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. *Cell* 153: 362–375, 2013
  7. Finsterbusch M, Hall P, Li A, Devi S, Westhorpe CL, Kitching AR, Hickey MJ: Patrolling monocytes promote intravascular neutrophil activation and glomerular injury in the acutely inflamed glomerulus. *Proc Natl Acad Sci USA* 113: E5172–E5181, 2016
  8. Dong X, Swaminathan S, Bachman LA, Croatt AJ, Nath KA, Griffin MD: Resident dendritic cells are the predominant TNF-secreting cell in early renal ischemia-reperfusion injury. *Kidney Int* 71: 619–628, 2007
  9. Dong X, Swaminathan S, Bachman LA, Croatt AJ, Nath KA, Griffin MD: Antigen presentation by dendritic cells in renal lymph nodes is linked to systemic and local injury to the kidney. *Kidney Int* 68: 1096–1108, 2005
  10. Snelgrove SL, Lo C, Hall P, Lo CY, Alikhan MA, Coates PT, Holdsworth SR, Hickey MJ, Kitching AR: Activated renal dendritic cells cross present intrarenal antigens after ischemia-reperfusion injury. *Transplantation* 101: 1013–1024, 2017
  11. Kawakami T, Lichtnekert J, Thompson LJ, Karna P, Bouabe H, Hohl TM, Heinecke JW, Ziegler SF, Nelson PJ, Duffield JS: Resident renal mononuclear phagocytes comprise five discrete populations with distinct phenotypes and functions. *J Immunol* 191: 3358–3372, 2013
  12. Satpathy AT, Kc W, Albring JC, Edelson BT, Kretzer NM, Bhattacharya D, Murphy TL, Murphy KM: Zbtb46 expression distinguishes classical dendritic cells and their committed progenitors from other immune lineages. *J Exp Med* 209: 1135–1152, 2012
  13. Odobasic D, Ghali JR, O'Sullivan KM, Holdsworth SR, Kitching AR: Glomerulonephritis induced by heterologous anti-GBM globulin as a planted foreign antigen. *Curr Protoc Immunol* 106: 15.26.1–15.26.20, 2014
  14. Schwarz M, Taubitz A, Eltrich N, Mulay SR, Allam R, Vielhauer V: Analysis of TNF-mediated recruitment and activation of glomerular dendritic cells in mouse kidneys by compartment-specific flow cytometry. *Kidney Int* 84: 116–129, 2013
  15. Heymann F, Meyer-Schwesinger C, Hamilton-Williams EE, Hammerich L, Panzer U, Kaden S, Quaggin SE, Floege J, Gröne HJ, Kurts C: Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. *J Clin Invest* 119: 1286–1297, 2009
  16. Evers BD, Engel DR, Böhner AM, Tittel AP, Krause TA, Heuser C, Garbi N, Kastenmüller W, Mack M, Tiegs G, Panzer U, Boor P, Ludwig-Portugall I, Kurts C: CD103+ kidney dendritic cells protect against crescentic GN by maintaining IL-10-producing regulatory T cells. *J Am Soc Nephrol* 27: 3368–3382, 2016
  17. Tadagavadi RK, Reeves WB: Renal dendritic cells ameliorate nephrotoxic acute kidney injury. *J Am Soc Nephrol* 21: 53–63, 2010
  18. Nelson PJ, Rees AJ, Griffin MD, Hughes J, Kurts C, Duffield J: The renal mononuclear phagocytic system. *J Am Soc Nephrol* 23: 194–203, 2012
  19. Lukacs-Kornek V, Burgdorf S, Diehl L, Specht S, Kornek M, Kurts C: The kidney-renal lymph node-system contributes to cross-tolerance against innocuous circulating antigen. *J Immunol* 180: 706–715, 2008
  20. Ng LG, Hsu A, Mandell MA, Roediger B, Hoeller C, Mrass P, Iparraguirre A, Cavanagh LL, Triccas JA, Beverley SM, Scott P, Weninger W: Migratory dermal dendritic cells act as rapid sensors of protozoan parasites. *PLoS Pathog* 4: e1000222, 2008
  21. Kassianos AJ, Sampangi S, Wang X, Roper KE, Beagley K, Healy H, Wilkinson R: Human proximal tubule epithelial cells modulate autologous dendritic cell function. *Nephrol Dial Transplant* 28: 303–312, 2013
  22. Ferenbach D, Hughes J: Macrophages and dendritic cells: What is the difference? *Kidney Int* 74: 5–7, 2008

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

## Mesenchymal Stromal Cells for AKI after Cardiac Surgery

Norberto Perico,<sup>1</sup> Federica Casiraghi,<sup>1</sup> and Giuseppe Remuzzi<sup>1,2,3</sup>

<sup>1</sup>IRCCS, Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; <sup>2</sup>Unit of Nephrology and Dialysis, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; and <sup>3</sup>Department of Biomedical and Clinical Sciences "L. Sacco," University of Milan, Milan, Italy

*J Am Soc Nephrol* 29: 7–9, 2018.

doi: <https://doi.org/10.1681/ASN.2017111207>

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

Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org).

**Correspondence:** Dr. Norberto Perico, IRCCS, Istituto di Ricerche Farmacologiche "Mario Negri," Clinical Research Center for Rare Diseases "Aldo & Cele Daccò," Via GB Camozzi 3, 24020 Ranica (Bergamo), Italy. Email: [norberto.perico@marionegri.it](mailto:norberto.perico@marionegri.it)

Copyright © 2018 by the American Society of Nephrology

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

Supported by the European Union's Horizon 2020 Research and Innovation Program under grant 634086 (Novel Stromal Cell Therapy for Diabetic Kidney Disease Study).

## REFERENCES

1. Wang Y, Bellomo R: Cardiac surgery-associated acute kidney injury: Risk factors, pathophysiology and treatment. *Nat Rev Nephrol* 13: 697–711, 2017
2. Xie X, Wan X, Ji X, Chen X, Liu J, Chen W, Cao C: Reassessment of acute kidney injury after cardiac surgery: A retrospective study. *Intern Med* 56: 275–282, 2017
3. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, Schaff HV: Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. *Crit Care* 15: R16, 2011
4. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group: KDIGO clinical practice guideline for acute kidney injury 2012. *Kidney Int Suppl* 2: 1–138, 2012
5. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, Bihorac A: Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* 119: 2444–2453, 2009

6. Ortega-Loubon C, Fernández-Molina M, Carrascal-Hinojal Y, Fulquet-Carreras E: Cardiac surgery-associated acute kidney injury. *Ann Card Anaesth* 19: 687–698, 2016
7. Sawhney S, Marks A, Fluck N, Levin A, McLernon D, Prescott G, Black C: Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. *Kidney Int* 92: 440–452, 2017
8. Morigi M, Benigni A: Mesenchymal stem cells and kidney repair. *Nephrol Dial Transplant* 28: 788–793, 2013
9. Perico L, Morigi M, Rota C, Breno M, Mele C, Noris M, Introna M, Capelli C, Longaretti L, Rottoli D, Conti S, Corna D, Remuzzi G, Benigni A: Human mesenchymal stromal cells transplanted into mice stimulate renal tubular cells and enhance mitochondrial function. *Nat Commun* 8: 983, 2017
10. Swaminathan M, Stafford-Smith M, Chertow GM, Warnock DG, Paragamian V, Brenner RM, Lellouche F, Fox-Robichaud A, Atta MG, Melby S, Mehta RL, Wald R, Verma S, Mazer CD; ACT-AKI investigators: Allogeneic mesenchymal stem cells for treatment of AKI after cardiac surgery. *J Am Soc Nephrol* 29: 260–267, 2018
11. Park M, Coca SG, Nigwekar SU, Garg AX, Garwood S, Parikh CR: Prevention and treatment of acute kidney injury in patients undergoing cardiac surgery: A systematic review. *Am J Nephrol* 31: 408–418, 2010
12. Gaspari F, Cravedi P, Mandalà M, Perico N, de Leon FR, Stucchi N, Ferrari S, Labianca R, Remuzzi G, Ruggenenti P: Predicting cisplatin-induced acute kidney injury by urinary neutrophil gelatinase-associated lipocalin excretion: A pilot prospective case-control study. *Nephrol Clin Pract* 115: c154–c160, 2010
13. Parikh CR, Thiessen-Philbrook H, Garg AX, Kadiyala D, Shlipak MG, Koyner JL, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Coca SG; TRIBE-AKI Consortium: Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of AKI after cardiac surgery. *Clin J Am Soc Nephrol* 8: 1079–1088, 2013
14. Yang X, Chen C, Teng S, Fu X, Zha Y, Liu H, Wang L, Tian J, Zhang X, Liu Y, Nie J, Hou FF: Urinary matrix metalloproteinase-7 predicts severe AKI and poor outcomes after cardiac surgery. *J Am Soc Nephrol* 28: 3373–3382, 2017
15. Chalmers J, Pullan M, Mediratta N, Poullis M: A need for speed? Bypass time and outcomes after isolated aortic valve replacement surgery. *Interact Cardiovasc Thorac Surg* 19: 21–26, 2014
16. Tögel FE, Westenfelder C: Kidney protection and regeneration following acute injury: Progress through stem cell therapy. *Am J Kidney Dis* 60: 1012–1022, 2012
17. Gooch A, Doty J, Flores J, Swenson L, Toegel FE, Reiss GR, Lange C, Zander AR, Hu Z, Poole S, Zhang P, Westenfelder C: Initial report on a phase I clinical trial: Prevention and treatment of post-operative acute kidney injury with allogeneic mesenchymal stem cells in patients who require on-pump cardiac surgery. *Cell Ther Transplant* 1: 31–35, 2008
18. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP: A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 16: 162–168, 2005
19. Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK, Ferguson TB, Peterson ED; Society of Thoracic Surgeons National Cardiac Surgery Database Investigators: Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation* 114: 2208–2216, 2006
20. Wijesundera DN, Karkouti K, Dupuis JY, Rao V, Chan CT, Granton JT, Beattie WS: Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. *JAMA* 297: 1801–1809, 2007
21. Birnie K, Verheyden V, Pagano D, Bhabra M, Tilling K, Sterne JA, Murphy GJ; UK AKI in Cardiac Surgery Collaborators: Predictive models for kidney disease: Improving global outcomes (KDIGO) defined acute kidney injury in UK cardiac surgery. *Crit Care* 18: 606, 2014
22. Casiraghi F, Remuzzi G, Abbate M, Perico N: Multipotent mesenchymal stromal cell therapy and risk of malignancies. *Stem Cell Rev* 9: 65–79, 2013
23. Ankrum JA, Ong JF, Karp JM: Mesenchymal stem cells: Immune evasive, not immune privileged. *Nat Biotechnol* 32: 252–260, 2014

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

H. Terence Cook and Matthew C. Pickering

Centre for Complement and Inflammation Research, Imperial College London, London, United Kingdom

*J Am Soc Nephrol* 29: 9–12, 2018.

doi: <https://doi.org/10.1681/ASN.2017111183>

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

Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org).

**Correspondence:** Prof. H. Terence Cook, Imperial College London, Du Cane Road, London W12 0NN, United Kingdom. Email: [t.cook@imperial.ac.uk](mailto:t.cook@imperial.ac.uk)

Copyright © 2018 by the American Society of Nephrology