Cell Therapy for Alport Syndrome

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Cell therapy for the treatment of human disease holds much promise, but few to date are standard of care. For regenerative medicine to be practicable, it is essential to have easily accessible sources of stem cells with high therapeutic potential. Advanced stem cell therapeutics aim to correct tissue or organ defects in a targeted manner by supplying stem cells that differentiate into the required cells in situ or are predifferentiated in vitro before infusion. Furthermore, it is critical that the cell preparation be safe and the method of delivery and patient preparation free of complications. In this issue of JASN, LeBleu et al. report on the use of different cell types for the treatment of Alport syndrome that are safe and efficacious.

Historically, many stem cell studies have shown efficacy in animals but used systems that were not conducive to clinical application. For example, introduction of genes into cells using viral vectors to trigger differentiation or to correct a mutation are successful in animal models, but their use in humans remains a source of concern. Similarly, for human embryonic stem (ES) cells to be used in patients, hurdles such as tissue matching, sourcing of cells, and the risk for teratomas need to be overcome. Some of these hurdles are circumvented by the production of induced pluripotent stem cells using removable vectors and the development of methods to prevent teratoma formation. Although many cell therapy studies are not suitable for clinical use, they are important to our understanding of stem cells and their role in treating disease. To date, the only stem cells used therapeutically are hematopoietic stem cells for bone marrow transplantation.

Cell-based therapies for the treatment of kidney disease have not been explored extensively. The current treatment for most kidney disease is dialysis or allogeneic kidney transplantation, but dialysis is not a permanent solution and donor organs are in short supply. Using the keywords “stem cell” and “kidney” to search the National Institutes of Health clinical trials web site, 186 clinical trials display, 184 of which are adjunctive therapies for kidney cancer using hematopoietic stem cells to replace patient bone marrow after aggressive chemotherapy or radiation.

See related article, “Proliferation and Migration of Label-Retaining Cells of the Kidney Papilla,” on pages 2315–2327.

REFERENCES


Published online ahead of print. Publication date available at www.jasn.org.

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search underscores the importance of the article by LeBleu et al., which contributes significantly to the early development of cell-based therapies for the treatment of Alport syndrome, a potentially fatal kidney disease affecting children and young adults.

The key finding in this new article is the demonstration of a beneficial effect on infusion of bone marrow (BM)-derived cells without the need for radiation preconditioning, which has been used in previous studies. The use of radiation before cell infusion has long-term adverse health issues for patients that may be a significant obstacle precluding treatment.6

Importantly, the article by LeBleu et al.1 demonstrates statistically significant improvement in kidney morphology and function in their animal model of Alport syndrome: Mice mutant for the α3 chain of type IV collagen treated with normal BM or peripheral blood (PB). They are also the first to report increased survival rates in test animals. LeBleu et al. found that COL4A3 mutant mice that had late-stage disease and received BM from normal mice improve over nontreated mice or mice receiving BM from COL4A3 mutant mice. Treatment of late-stage disease is critical, because many current stem cell interventions aim to prevent the progression of a disease, which limits therapy to patients with newly diagnosed disease.7

What is the possible explanation for these results? The authors demonstrate the integration of transplanted BM cells into kidney tissue and the expression of kidney-specific markers, suggesting transdifferentiation or possibly cell fusion has occurred. Although they do not explore which mechanism it is, the study suggests infused cells are capable of migrating to damaged tissue and repairing it. Interestingly, these studies confirm findings from other systems showing infused cells capable of homing to sites of injury, most likely as a result of local inflammation, which in turn results in the release of cytokines that attract implanted cells.8 This report also demonstrates that donor cells, through the production of a normal α3(IV) protein, reconstitute the α3α4α5(IV) protomer and restore proper kidney function in Alport mice. This positive result, achieved without radiation, clearly demonstrates the ability of BM or PB cells to repair tissue through the production of the missing protein. These results are in contrast to those of Katayama and colleagues,9,10 who showed radiation alone improves kidney function. Although these latter studies were not able to demonstrate the production of the missing α3(IV) protein, kidney function improved in treated mice. Such positive results could be explained by the production of an alternative protomer consisting of α5α6α5(IV) that rescues the Alport phenotype.

Eliminating the need for radiation preconditioning has advantages and disadvantages. Without preconditioning, blood cells are unable to engraft BM permanently, and the resultant turnover of implanted cells in the kidney may eventually result in the loss of the therapeutic effect. Although multiple infusions during the lifetime of the patient may compensate for this attrition, a supply of matched blood cells is always difficult to procure. Regardless of these potential problems, nonradiation treatment may still be the choice, because it is safer, and, to date, there is no evidence that permanently engrafted donor blood cells will migrate from the BM and home to the damaged kidney to keep it in good repair.

Although engrafted cells only composed 3% of each glomeruli, LeBleu et al.1 still demonstrate marked improvement in kidney function. Is it possible these few cells produce α3(IV) protein at an increased rate as a result of regulatory signals from the surrounding cells? The authors point out some of the improvement may come from infused cells activating endogenous kidney stem or progenitor cells. This explanation is echoed by Gross et al.,11 who reported that the use of mesenchymal stem cells (MSCs) from BM have a positive effect on Alport mice without actually differentiating into glomerular or tubular cells. They attribute improvement to an indirect mechanism whereby the MSCs secrete growth factors, which might act on endogenous cells and aid, at least partially, in restoring kidney morphology and function. This contention is supported by the study by LeBleu et al.,1 because PB works as well as BM, strongly indicating that mesenchymal cells are not the source of cells providing the improvement; mesenchymal cells are not present at high enough numbers in PB to explain the observation.

The mouse and human ES cell results reported in the study by LeBleu et al.1 are also intriguing (human ES cells were transferred into COL4A3/Rag-1 DKO mice). Although the authors demonstrate that mouse ES cells differentiate in vitro into podocyte-like cells, these differentiated cells do not show the glomerular tuft or engraft, whereas undifferentiated ES cells do, resulting in improved function. Although not explained in the article, these results are intriguing and suggest undifferentiated ES cells are capable of homing to the site of kidney damage and receive signals from the kidney that trigger proper, controlled differentiation. Similar to the blood cells, it is possible that cell fusion explains the presence of ES-derived podocytes.

Taken together, the results presented here are highly provocative. As reported by other groups, the transdifferentiation of PB or BM cells or the presence of an embryonic-like stem cell in blood or BM usually cannot account for the high level of tissue regeneration observed. Indirect mechanisms of repair, such as the possibility that infused cells act as a source of cytokines and growth factors, adds to this important emerging body of work.

The conclusion of the article by LeBleu et al.1 is that various cell sources—bone marrow, blood, or embryonic stem cells—are capable of reversing the effects of kidney disease. Although the article’s title refers to stem cell–based therapies for Alport syndrome, these fascinating results indicate the key cells are likely mature cells, because PB used throughout this study to generate positive results does not contain appreciable MSCs or hematopoietic stem cells. LeBleu et al. do not identify the important cells transferred but are able to eliminate possible candidates. Their embryonic
stem cell data are significant because they suggest that undifferentiated ES cells are also capable of contributing to regeneration by providing the missing α3(IV) chain in a manner similar to the blood and BM cells.

Although the successful treatment of mice, including increased survival rates, is significant, it is still a big step to use such stem cells in clinical trials. This article, however, represents significant movement toward the development of cell-based therapies for the treatment of kidney disease and has implications beyond Alport syndrome.

DISCLOSURES
None.

REFERENCES


Critical Care Nephrology: It’s Not Just Acute Kidney Injury
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The care of the critically ill with kidney disease represents a growing proportion of patients treated by nephrologists in the hospital. As a result, critical care nephrology, melding together the expertise of nephrologists and intensivists, has emerged as a distinct subdiscipline during the past decade.1–3 Critical care nephrology is a topic at national and international meetings, has a proposed core curriculum for trainees,4 and even has its own textbook;5 however, a casual perusal of the literature in critical care nephrology rapidly reveals an almost exclusive focus on issues pertaining to acute kidney injury (AKI) with relative neglect of the patient with ESRD and superimposed critical illness. In a nearly 1800-page textbook of critical care nephrology, discussion of critically ill patients with ESRD are covered in fewer than a dozen pages.3

The need for critical care nephrology to broaden its perspective and provide increased focus on patients who have ESRD and are critically ill is highlighted by the findings of Strijack et al. in this issue of JASN.6 Using a prospectively maintained database of all adult patients admitted to intensive care units (ICUs) in Winnipeg, Manitoba, Canada, they found patients with ESRD accounted for nearly 3.4% of all ICU admissions and estimated the annual rate of ICU admission among adult patients with ESRD was more than 25 times that of the general adult population. The ESRD patients were younger, less likely to be male, and more than twice as likely to have diabetes as compared with the general ICU population. Although rates of coronary artery disease were similar, patients with ESRD had more than two-fold the rate of peripheral vascular disease, were more likely to require ICU care for nonsurgical disease, had more than double the rate of sepsis than the general ICU population, and had substantially higher severity of illness scores, even after subtracting the renal component. The patients with ESRD composed nearly 40% of patients who received renal replacement therapy (RRT). The remainder, representing patients with AKI, had even higher severity of illness scores with more than double the frequency of sepsis as compared with the patients with ESRD. Overall hospital mortality was ap-