

High-Molecular Weight Iron Dextran: A Wolf in Sheep's Clothing?

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J Am Soc Nephrol 19: 833–834, 2008.
doi: 10.1681/ASN.2008020224

Parenteral iron is given to patients in a variety of formulations, including two iron dextran products known as high- (HMW) or low- (LMW) molecular weight iron dextran. Despite more risk of adverse events, HMW iron dextran is sometimes substituted for LMW iron dextran without physician knowledge for reasons of cost. A recent decision by the Centers for Medicare and Medicaid Services (CMS) to re-merge J-codes for both iron dextrans may increase the unintended use of HMW iron dextran, resulting perhaps in more adverse drug events. Physicians who use parenteral iron should be aware of these practices and actively participate in formulary decisions regarding their substitution.

Recently, in Tennessee, a physician ordered LMW iron dextran (INFeD, Watson, Morristown, NJ) in a patient for iron deficiency anemia when oral iron had been ineffective and tolerated poorly. The pharmacist substituted the less expensive HMW iron dextran (Dexferrum, American Regent, Shirley, NY). Anaphylaxis shortly after receiving a test dose of HMW iron dextran was followed by death. Despite at least nine publications demonstrating higher rates of adverse drug events with HMW iron dextran^{1–9} and with no publications showing contradictory results, HMW iron dextran continues to be substituted by individuals seemingly unaware of the various risk profiles among products for intravenous iron replacement. In one of these studies, the adverse event rate following administration of HMW iron dextran was 28%.⁵ The reported total absolute rates of adverse drug events with parenteral iron are 38 per million doses, with life-threatening adverse drug events per million

of 11.3 for HMW iron dextran, 3.3 for LMW dextran, 0.9 for ferric gluconate, and 0.6 for iron sucrose.¹⁰ Even more worrisome is the ready substitution of HMW for LMW iron dextran because of cost, which is not a rare event. We have personally documented such occurrences where clinicians ordered LMW iron dextran and HMW iron dextran was substituted in its place. In four confirmed instances where anaphylaxis did not result in death, LMW iron dextran was subsequently administered uneventfully.

By the early 1990s, intravenous iron was used routinely to synergize with erythropoiesis stimulating agents (ESAs) for the treatment of dialysis-associated anemia. LMW and HMW iron dextrans were the only products available throughout the 1990s. In 1997, LMW iron dextran became unavailable for several months, necessitating the use of HMW iron dextran in virtually all dialysis patients requiring intravenous iron to support erythropoiesis. During that period, there was an 1100% increase in adverse drug events reported to the Food and Drug Administration (FDA) following administration of iron dextran according to data obtained through the Freedom of Information Act (obtained by M.A.). Subsequently, in 1998, the FDA declared LMW iron dextran “medically necessary” despite the widespread availability of the HMW product. The FDA definition of medically necessary is, “. . . if the product is used to treat or prevent a serious medical condition, and there is no other source of that product or alternative drug that is judged by medical staff to be an adequate substitute.” Today, other parenteral iron products are also relatively safer, including ferric gluconate and iron sucrose, although more expensive.

In the first study to demonstrate the benefits of intravenous iron when used in conjunction with ESAs for chemotherapy-induced anemia, 79 patients received LMW iron dextran and two patients received HMW iron dextran.⁹ Although none of the 79 patients receiving LMW iron dextran experienced a serious adverse drug event, one of the two patients who received HMW iron dextran experienced anaphylaxis requiring intubation. Using data from the FDA MedWatch program, Chertow *et al.*³ determined that the rates of all, as well as life-threatening, adverse drug events were significantly higher among recipients of HMW *versus* LMW iron dextran or other nondextran iron products. Moreover, using conservative assumptions about the distribution of “iron dextran-associated” adverse drug events where product was not specified, the authors suggest the higher event rate observed with HMW iron dextran may be an underestimate. There also are two published studies in hemodialysis patients comparing LMW iron dextran to iron sucrose,^{10,11} generally considered by nephrologists to be safer than iron dextran, showing some¹⁰ or no difference in toxicity.¹¹

In 2006, different J-codes, which are drug-specific codes used to bill CMS, were assigned to Dexferrum (HMW) and INFeD (LMW) iron dextrans. Providing dif-

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

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ferent J-codes forced providers to discriminate between these products and allowed better tracking of drug-specific adverse reactions. In January 2008, CMS re-merged the J-codes for HMW and LMW iron dextran. For the majority of U.S. physicians who are unaware that two iron dextrans even exist, there is high likelihood that the lower-priced HMW iron dextran will be selected by group purchasing organizations for distribution to ambulatory infusion centers and hospitals. As a result, physicians may unknowingly administer the HMW iron dextran, thereby increasing the likelihood of life-threatening, preventable adverse events. This substitution could accentuate the underutilization of intravenous iron that abounds already because of misinterpretation and misunderstanding of the incidence and nature of serious adverse events largely associated with HMW iron dextran. Given so much uncertainty surrounding the safety of ESAs in oncology as well as in nephrology practices, decreased utilization of intravenous iron would be counterproductive. There are now five publications in the oncology literature (three published and two in press),^{9,12–15} demonstrating intravenous iron synergizes with ESAs in improving hemoglobin responses, decreasing the time to target hemoglobin and subsequently decreasing ESA exposure and cost of therapy. In all five of these studies, the benefits were independent of the pretreatment baseline iron parameters, including Fe/TIBC, ferritin, and bone marrow hemosiderin.

All countries in Western Europe have halted distribution of HMW iron dextran and removed the black box warning from the package insert or equivalent documents for the LMW formulation. The clinical community's larger perception of risk associated with the use of intravenous iron is antiquated and probably incorrect. While adverse event rates are driven higher by HMW iron dextran, both HMW and LMW iron dextrans, and to a lesser extent all intravenous iron formulations, suffer this stigma. HMW iron dextran is unsafe compared with other iron products and is medically unnecessary given the availability of three safer products in the United States. We urgently recommend avoiding use of HMW iron dextran in all clinical practice settings. We also recommend that the FDA withdraw this formulation of intravenous iron. Additional research into the optimal use of parenteral iron, particularly among persons treated with ESAs, is clearly warranted.

DISCLOSURES

Drs. Rodgers, Cella, Chertow, and Glaspy have nothing to disclose. Drs. Auerbach, Coyne, and Henry are consultants for Watson Pharmaceuticals, and Dr. Coyne has received research support from Watson Pharmaceuticals.

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Some Assembly Required: Renal Hypodysplasia and the Problem with Faulty Parts

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J Am Soc Nephrol 19: 834–836, 2008.
doi: 10.1681/ASN.2008030281

Renal hypodysplasia encompasses a broad spectrum of disorders that are all characterized by varying degrees of defective kidney formation. Dysplastic kidneys exhibit multiple types of pathology,^{1,2} with defects evident as cystic tubule dilation, fibrosis, and dysregulated cell proliferation and cell death.² Renal hypodysplasia is characterized by a reduced number of nephrons, with compensatory changes in glomerular size driven by increased single-nephron GFR.² Overall, renal hypodysplasia is a leading cause of pediatric renal failure and can contribute to the development of hypertension in adults.³

In the search for genes that cause renal hypodysplasia, the link to renal development is compelling: What better candidate gene for a kidney that does not fully develop than a gene required for development? Kidneys form during embryogenesis by a tissue interaction between a ureteric bud epithelium and a loose population of stromal cells in the metanephric mesenchyme.⁴ The information required to orchestrate kidney growth and development is passed between these two tissues in the form of secreted growth factors and growth factor antagonists. The dynamic interplay of secreted molecules that promote and inhibit epithelial outgrowth, along with the activity of transcription factors that regulate growth factor expression, shapes the tree-like architecture of the collecting system, drives initial nephron formation, defines overall kidney organ size, and determines the final number of nephrons in the mature kidney.⁴ The RET/glial-derived neurotrophic factor (GDNF) signaling interaction is a central regulator of kidney morphogenesis. GDNF is a diffusible growth factor that is synthesized in the mesenchyme and binds to its receptor Ret on the ureteric bud epithelium and drives growth and patterning of the collecting system.⁵

Previous studies linking mutations in well-studied kidney developmental regulators to renal hypodysplasia have encouraged the search for other regulatory genes that might be associated with this disease. The hereditary disorders renal coloboma syndrome (PAX2), renal cysts and diabetes syndrome (HNF-1 β), and branchio-oto-renal syndromes (EYA1) all link mutations in developmental regulatory transcription factors with renal hypodysplasia.² Recent studies examining the GDNF and RET genes in cases of severe hypodysplasia have turned up multiple activating and inactivating mutations.⁶ Still, mutations in *RET*, *GDNF*, *PAX2*, *HNF1 β* , and *EYA1* do not account for all cases of renal hypodysplasia. The Fraser syndrome gene *FRAS1* (not to be confused with Frasier syndrome/WT1 mutations) and *glypican-3* (*GPC3*) both are mutated in renal hypodysplasia and encode proteins that might be expected to modulate or control the activity of other secreted kidney developmental regulators such as bone morphogenetic proteins (BMP) or fibroblast growth factors.² These findings

beg the question of whether additional developmental signaling molecules mutate in patients with renal hypodysplasia.

In this issue of *JASN*, Weber *et al.*⁷ identify new mutations in the gene encoding *BMP4* and the transcriptional regulator *SIX2* associated with renal hypodysplasia. *BMP4* is a member of the BMP family, which comprises a subgroup of proteins within the TGF- β superfamily. *BMP4* has complex functions in kidney development, including restricting the site of initial budding of the ureter to form a single ureter, support of smooth muscle development around the ureter, and promoting growth and survival of nephrogenic mesenchyme.^{8,9} *SIX2* is a transcription factor whose expression in the renal mesenchyme is required for synthesis of GDNF.¹⁰ The association of missense mutations in these genes with renal hypodysplasia provide new potential links between development and disease; however, proving that the missense mutations are causal for the disease is another story.

Despite the wealth of data from genetic studies of kidney development for use in generating candidate genes for renal hypodysplasia, pinpointing disease-causing mutations in human syndromes often requires more than standard linkage analysis and sequencing. The main challenge is to assign biologic significance to what might be subtle missense mutations. For instance, how do you interpret a glycine to valine substitution? Is the addition of a single methyl group to a protein sufficient to disrupt its function? Or is this just a polymorphism? The short answer is, you don't know. Missense mutations, as opposed to more severe nonsense mutations, are the most common type of mutation associated with human disease. This trend is likely only to become more pronounced in current and future studies of complex, polygenic diseases for which disease severity is likely associated with a combination of missense mutations in several different genes; that is, the "mutational load" will determine many disease outcomes. When regulators of basic developmental processes are your best candidate genes, missense mutations that render a protein partially functional are likely to be the only types of mutations found, because anything more nasty would end things *in utero*. What is needed in this context is a reliable way to assess the function of a subtly altered protein.

Designing *in vitro* assay systems for mutant genes can be a trial-and-error process; developmental context is often important for molecular function, and mouse knock-ins to test multiple allelic variants can be prohibitively expensive. So why bother with assay development when Mother Nature has already done it for you? The fish embryo is an *in vivo*, self-contained, and sensitive assay system for any signaling pathway that is important in development.¹¹ Weber *et al.*⁷ exploit this to show that missense alleles of human renal hypodysplasia genes show an altered function in the context of zebrafish embryogenesis, strengthening their argument that the missense mutations they identified are causative for disease. Comparative analysis using fish embryos to sort through candidate genes for human disease and to assay human mutant alleles has also been useful in other disease contexts^{12–17}; Weber *et al.*⁷ show that

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

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this approach can be particularly useful in studies of renal hypodysplasia.

Although these studies demonstrate a new use of the zebrafish embryo for assessing the severity of human hypodysplasia mutations, there is still room for improvement in this general approach. The method used by *Weber et al.*⁷ relies on overexpression of proteins during developmental stages and in cells in which the normal endogenous protein would not be expressed. This forced expression is the reason that developmental defects are observed, even though the normal protein—and not mutant protein—is being expressed. Would these proteins act in the same way when expressed in their normal context? The assumption is yes, they would, but it will be important in future studies to demonstrate this directly. For instance, expression of mammalian genes in zebrafish embryos has been used to reverse or rescue zebrafish mutant phenotypes.¹² Would wild-type but not mutant mRNA encoding human *SIX2* or *BMP4* rescue zebrafish mutants in these genes? If so, then the experiments would be one step closer to assaying these genes in a normal developmental context. With either approach, it will also be important to confirm the expression of introduced mutant and wild-type proteins to avoid the potential pitfall that lack of observable effects could simply be due to reduced expression of mutant protein.

Zebrafish kidneys are not human kidneys, but the conservation of developmental mechanisms used to build them (and other organs) is remarkable.¹⁸ On the basis of the work of *Weber et al.*⁷ and other, similar studies, the fish embryo now occupies an experimental niche uniquely positioned between human hereditary disease pathology and cell culture assays of mutant genes. Genetic manipulation of the fish embryo coupled with careful, quantitative analysis of phenotypes is now an established way to assay gene function rapidly, *in vivo*, in a relevant developmental context.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (DK071041).

I thank members of my laboratory, Yan Liu and Sasha Petrova, for critical review.

DISCLOSURES

None.

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See related article, “*SIX2* and *BMP4* Mutations Associate With Anomalous Kidney Development,” on pages 891–903.

Perinatal Nephron Programming Is not So Sweet in Maternal Diabetes

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J Am Soc Nephrol 19: 837–839, 2008.
doi: 10.1681/ASN.2008030280

Development of the permanent, metanephric kidney begins at approximately embryonic day 11 (E11) in mice, E12 in rats, and during the fourth through fifth gestational weeks in humans. During these stages, the ureteric bud projects from the mesonephric duct and enters the metanephric anlage, whereupon buds branch repeatedly and ultimately form the collecting duct system of the mature kidney (and urothelium, including the renal pelvis, ureters, and bladder trigone). At the inception of nephrogenesis, metanephric mesenchymal cells are attracted to and condense around each tip of an advancing ureteric bud branch. Shortly after condensation, the mesenchyme then converts to polarized epithelia, which proceeds through an orderly sequence of nephric structures (termed vesicle, comma- and s-shaped, developing capillary loop, and glomerular stages) that eventually constitute the mature nephron. These nephrogenic processes of ureteric bud growth and branching, mesenchymal cell induction and aggregation, conversion to epithelia, and glomerular differentiation and tubule elongation occur repeatedly until there is a full complement of nephrons. Nephrogenesis concludes approximately 1 wk after birth in rodents and during the 34th gestational week in humans.

Considerable progress has been made in understanding many of the molecular details that underlie the induction of nephrogenesis, and only a few of them can be mentioned here. For example, the “paired box” transcription factor-2 (*Pax2*) first appears during the caudal descent of the nephric duct, then expresses in uninduced and induced metanephric mesenchyme, where it stimulates expression of glial cell–derived neurotrophic factor,¹ and also expresses in ureteric bud epithelia, where it suppresses apoptosis. *Pax2* also increases expression of *Wnt-4*, a secreted glycoprotein that activates the β -catenin signaling pathway regulating cell growth.² The transcription factor *WT1* is expressed in uninduced mesenchyme but is sharply upregulated as cells condense around ureteric bud branches. *Wnt-4* is also upregulated in condensing mesenchyme and, together with *WT1*, expresses through the vesicle and comma- and S-shaped stages, suggesting both of these

proteins are key mediators of epithelial differentiation. One of the gene products directly regulated by *WT1* is *Pax2*, which becomes downregulated during s-shaped stages of nephron development.³ Similarly, reciprocal expression of the receptor tyrosine kinase *Ret* and its ligand, glial cell–derived neurotrophic factor, by ureteric bud epithelia and metanephric mesenchyme, respectively, induces and maintains ureteric bud branching morphogenesis.¹ As the condensed metanephric mesenchymal cells serially convert to epithelia, the expression of a host of mesenchymal proteins (*e.g.*, neural cell adhesion molecule, vimentin, types I and III collagen) are suppressed, whereas proteins that typify epithelia (*E-cadherin*, cytokeratin, type IV collagen, and laminin) all upregulate.

Although much has been learned about the induction of nephrogenesis, considerably less is known about mechanisms that conclude the process. Nevertheless, many factors contribute to final nephron endowment, including the extent of ureteric bud elongation and branching, conversion of mesenchyme to epithelia, maintenance of the epithelial nephric figures, and overall rates of metanephric mitosis and apoptosis; some of the genetic regulators of these processes have already been summarized. Furthermore, unbiased stereologic methods show mature human kidney can average from as few as approximately 200,000 to nearly 2 million nephrons.⁴ This wide variation in nephron endowment may have profound consequences, however, and there is increasing evidence that individuals with reduced nephron number are prone to develop hypertension, renal failure, and/or other cardiovascular disorders later in life. Notably, mice with a complete absence of *Pax2* lack the caudal portion of the Wolffian duct, from which the ureteric bud originates, and are therefore anephric.⁵ Humans who are heterozygous for *Pax2* mutations have renal coloboma syndrome, which results in ocular colobomas, renal hypoplasia, and renal failure in childhood.⁶ Additional evidence shows heterozygous mutations of *Pax2* in mice also result in loss of renal mass with increased apoptosis and decreased branching of the ureteric bud, leading to significantly fewer nephrons.⁶

Several different genetic mutations cause renal growth disorders,^{7,8} but there are also many important—and possibly much more prevalent—environmental causes. A growing body of data in humans and experimental animals indicates that maternal malnutrition, placental insufficiency, fetal exposure to certain medications and other toxins, inhibition of the renin-angiotensin system, and/or vitamin A (retinoid) depletion all can result in low birth weight.⁹ Although this may not always affect nephron endowment, in many cases low birth weight correlates inversely with a tendency for the development of hypertension, proteinuria, and metabolic syndrome in adulthood.⁹ Increasingly, the Barker hypothesis (adult disease has fetal origins), as it relates to certain renal functional abnormalities in maturity, attributes at least some of the harm to events taking place specifically during kidney organogenesis, which in humans normally occurs exclusively *in utero*.

Maternal hyperglycemia can similarly induce a wide range of developmental abnormalities affecting multiple organ systems in the fetus (diabetic embryopathy), including kidney.^{10,11} Indeed, women with pregestational diabetes and fasting hyperglycemia

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

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have at least a three- to four-fold increased risk for infant malformations.¹² Metabolic changes accompanying chronic hyperglycemia in patients with diabetes include abnormal myoinositol and diacylglycerol levels, stimulation of protein kinase C, nonenzymatic glycation of intracellular and extracellular proteins, and increased production of reactive oxygen species, all of which can progressively damage a wide variety of tissues.¹¹ Unusually susceptible to injury are molecules with relatively slow turnover, such as DNA and collagen, and one of the hallmarks of diabetes in adults is excessive accumulation and abnormal cross-linking of basement membrane proteins, particularly in renal glomeruli and other vascular structures. In pregnant women with poorly controlled pregestational diabetes, the fetus is exposed to elevated glucose levels throughout pregnancy, including the several weeks after conception, when many developmental processes are especially vulnerable. For example, caudal regression syndrome is a relatively rare congenital defect associated with an absence of the sacrum and defects of the lumbar spine and with a variety of malformations of the lower limbs and central nervous, cardiovascular, gastrointestinal, musculoskeletal, and genitourinary systems. Although the genetic anomaly is undefined, caudal regression syndrome is at least 250 times more prevalent in diabetic pregnancies.¹³ Furthermore, studies in diabetic pregnant mice showed they are significantly more prone to generate embryos with caudal regression when they are treated with all-*trans* retinoic acid, a widely known teratogen.¹³ These findings suggest maternal diabetes together with environmental factors operate synergistically to potentiate diabetic embryopathy.¹³

A number of studies have examined the adverse effects of hyperglycemia on nephrogenesis specifically. Marked decreases in nephron induction and tubulogenesis are observed when rat metanephroi grown in organ culture are treated with high (30 mM) D-glucose as compared with normal (5 mM) D-glucose.¹⁴ In organ cultured mouse metanephroi,¹⁵ and *in vivo*,¹⁶ high glucose induces excessive *Pax2* gene expression through generation of reactive oxygen species and activation of the NF- κ B pathway, which also mediates inflammatory responses and apoptosis. In this issue of *JASN*, new details are provided on the detrimental nephrogenic effects of maternal hyperglycemia.¹⁷ Offspring of diabetic mice have significantly lower body weight, body size, kidney weight, and fewer nephrons than pups from nondiabetic controls. In addition, kidneys from offspring of diabetic mice have increased expression of mRNA encoding angiotensinogen and renin and nuclear localization of the NF- κ B isoforms p50 and p65. Importantly, there is also evidence for increased glomerular and tubular apoptosis in kidneys from mice born of diabetic mothers, which may represent the ultimate explanation for reduced nephron endowment in these animals.

Given the relatively lengthy period in which the human kidney undergoes nephrogenesis (from the fourth/fifth gestational week to week 35), perhaps restoration of normal glycemic control from mid- to late-gestational periods can minimize adverse effects of maternal hyperglycemia on kidney development. Along these lines, one study using a growth-restricted, placental insufficiency model found that cross-fostering growth-restricted pups postnatally

using normal lactating dams corrected loss of renal endowment and prevented the development of hypertension.¹⁸ Conversely, another study reported that even a brief infusion of glucose into pregnant rats at the inception of nephrogenesis (from E12 to E16) resulted in significant nephron deficits 2 wk after birth.¹⁹ In view of the expanding epidemic of diabetes, a much larger population of infants and mothers will undoubtedly become at risk to the hazards and complications of hyperglycemia during pregnancy.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grant DK065123.

DISCLOSURES

None.

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See related article, “Maternal Diabetes Modulates Renal Morphogenesis in Offspring,” on pages 943–952.

Toward the Promise of Renal Replacement Therapy

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J Am Soc Nephrol 19: 839–840, 2008.
doi: 10.1681/ASN.2008030291

In this issue of *JASN*, Tumlin *et al.*¹ report results of a revolutionary phase 2 multicenter, randomized clinical trial comparing 72 h of continuous venovenous hemofiltration (CVVH) with and without a bioartificial kidney (referred to as a renal tubule assist device [RAD]) in the management of severe acute kidney injury. Fifty-eight patients were randomly assigned: 40 to CVVH + RAD and 18 to CVVH alone. Multiple outcomes were evaluated, including the standard metric for clinical trials in critical care with 28-d survival as the primary outcome. All-cause mortality at 90 and 180 d, time to recovery of kidney function, time to intensive care unit and hospital discharge, and safety parameters were also examined. Mortality rates at 28 and 180 d were marginally lower among patients who were randomly assigned to CVVH + RAD.

One could easily criticize aspects of the design, implementation, and analysis of the trial and its reporting. First, there was no documentation of the expected effect size, except in the context of the investigators’ estimated improvement (stratified as <10, 10 to 23.3, and >23.3%) that would guide the conduct of subsequent

trials. Regardless, the study was hopelessly underpowered. If one were to consider a comparison of two strategies directed toward the management of severe acute kidney injury in the intensive care unit and estimate the 28-d mortality in CVVH-treated patients at the midpoint of the range cited by the authors (60%), the sample size required to detect a reasonable and clinically meaningful reduction in mortality (10% absolute, 16.7% relative) would be 768 with 80% power or 1028 with the 90% power typically recommended for substantive interventions. Corresponding sample sizes would be 188 and 252 with a larger, arguably unrealistic effect estimate (20% absolute, 33% relative). Of note, these sample size estimates do not account for loss to follow-up or dropout. We previously highlighted the pitfalls of conducting underpowered clinical trials, even when results are conventionally significant.²

Second, only 10 of 40 patients who were randomly assigned to CVVH + RAD completed the planned 72 h of therapy. The rationale for discontinuing the RAD intervention for clinical improvement or deterioration was not provided.

Third, the primary result (28-d mortality in 13 [33%] of 39 CVVH + RAD—versus 11 [61%] of 18 CVVH alone—treated patients) was not statistically significant and failed to consider the patient who was assigned to CVVH + RAD and died before RAD therapy was instituted; that is, the comparison was performed in an as-treated rather than an as-randomized “intention-to-treat” sample.³

Fourth, at least seven outcomes were assessed (death at three discrete time points, recovery of kidney function at two discrete time points, and time to death and time to recovery of kidney function) without consideration of the statistical implications of multiple comparisons. Moreover, the authors failed to offer a compelling hypothesis for why a nonsignificant effect in the short term might be expected to produce a significant benefit in the longer term, particularly when the intervention lasted at most 72 h. Finally, numerous nonprespecified subgroup analyses were conducted; for example, with and without sepsis or with higher and lower APACHE II and SOFA scores.

Despite these limitations, the investigators should be commended for having extraordinary vision, courage, and creativity to invent and legitimately test a bioartificial renal device. Although conventional dialysis technologies have been developed and refined with the primary goal of enhancing the clearance of metabolic waste, hazardous electrolytes, and excess extracellular fluid, they have failed to address many, if not most, of the broad-ranging functions of the kidney, as the authors articulate. Although some investigators have questioned whether critically ill patients die *with* or *from* acute kidney injury, epidemiologic evidence strongly suggests that patients with acute kidney injury experience an excess of death directly attributable to the kidney injury itself,^{4–6} although it seems unlikely that azotemia, hyperkalemia, hypervolemia, or other dialysis-remediable abnormalities are culpable. Indeed, one might look toward the dialysis *versus* transplantation experience in ESRD as an informative analogy.

The provision of dialysis itself, although sustaining life, fails to restore health to the majority of patients who have ESRD. Patients who have ESRD and receive a kidney transplant enjoyed markedly prolonged survival and enhanced health-related quality of life relative to patients who remain on dialysis, despite the multiplicity of assaults on

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

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the transplanted kidney and its recipient: ischemia reperfusion injury, low nephron mass of the allograft, and immunosuppressive therapies that result in impaired kidney function, insulin resistance, dyslipidemia, osteoporosis, and increased risks of opportunistic infections and malignancy. It should be no surprise, then, that an analogous approach in acute kidney injury—that is, dialysis or hemofiltration to remove water-soluble metabolic wastes, salt, and water—might not achieve resounding or complete biologic success.

The incidence of acute kidney injury requiring dialysis is rising, and although large population-based studies suggested that outcomes may have improved marginally in the past 15 yr, rates of death and nonrecovery remain unacceptably high.^{7–9} Altering our approach to the modality or dosage of dialysis or hemofiltration has yielded inconsistent and conflicting results.^{10–14} While we anxiously await the results of the Veterans Affairs– and National Institutes of Health–sponsored Acute Renal Failure Trial Network (ATN) study,¹⁵ a comparison of intensive *versus* less intensive hemodialysis or hemodiafiltration in severe acute kidney injury, additional attempts at restoring some of the vital (noninert) aspects of kidney function to critically ill patients needs encouragement. Regardless of whether this particular iteration of the bioartificial kidney ultimately achieves success in clinical trials, this effort represents a landmark event in the history of nephrology. The authors should be celebrated for their efforts.

DISCLOSURES

None.

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See related article, "Efficacy and Safety of Renal Tubule Cell Therapy for Acute Renal Failure," on pages 1034–1040.

The Appearance of Brief Communications in JASN

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J Am Soc Nephrol 19: 840, 2008.
doi: 10.1681/ASN.2008030255

With this issue of *JASN*, we introduce a new feature for original manuscripts, the Brief Communication. These articles are short, about 1500 words, and written in letter format followed by concise methods and no more than four figures; some of the dataset may be submitted supplemental to the manuscript. For a while we have felt such an outlet might stimulate the submission of interesting or novel findings where an expanded story will have to follow from subsequent work. Will our reviewers be able to adapt to evaluating less than is expected for a full-length manuscript? It remains to be seen. The editors expect a good story well supported by controlled data and some insight into mechanism. This is a tall order for authors in the limited space available for such letters, but other well-regarded journals attract such submissions. So far, we have declined a number of offerings, and with this issue start with two manuscripts surviving review and much revision. We hope this new feature will be used wisely and add value to the wonderful content already in our pages. Details for submitting Brief Communications can be found in the instructions to authors. Submissions should be labeled as such.

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

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