Challenges and Advances in the Treatment of AKI

Gur P. Kaushal and Sudhir V. Shah

Division of Nephrology, Department of Internal Medicine, University of Arkansas for Medical Sciences and Renal Section, Medicine Service, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas

ABSTRACT
Treating or preventing AKI requires treating or preventing a rise in serum creatinine as well as the immediate and remote clinical consequences associated with AKI. Because a substantial number of patients with AKI progress to ESRD, identifying patients likely to progress and halting progression are important goals for treating AKI. Many therapies for AKI are being developed, including RenalGuard Therapy, which aims to maintain high urine output; α-melanocyte–stimulating hormone, with anti-inflammatory and antiapoptotic activities; alkaline phosphatase, which detoxifies proinflammatory substances; novel, small interfering RNA, directed at p53 activation; THR-184, a peptide agonist of bone morphogenetic proteins; removal of catalytic iron, important in free-radical formation; and cell-based therapies, including mesenchymal stem cells in vivo and renal cell therapy in situ. In this review, we explore what treatment of AKI really means, discuss the emerging therapies, and examine the windows of opportunity for treating AKI. Finally, we provide suggestions for accelerating the pathways toward preventing and treating AKI, such as establishing an AKI network, implementing models of catalytic philanthropy, and directing a small percentage of the Medicare ESRD budget for developing therapies to prevent and treat AKI and halt progression of CKD.

WHAT DOES TREATMENT OF AKI MEAN?

The diagnosis of AKI is based on a rise in serum creatinine; for clinicians and researchers, a cure would represent preventing or treating the rise in serum creatinine. However, the US Food and Drug Administration (FDA) does not consider an agent that prevents an increase in serum creatinine sufficient evidence to register it as a drug. The FDA focuses on clinical outcomes rather than changes in laboratory values. The FDA’s position, with good justification, is that although we have known that an increase in serum creatinine is associated with poor outcomes, we have not established that poor outcomes are a result of an increase in serum creatinine. Thus, it is important that when we think of treating AKI, we think not only of preventing or treating a rise in serum creatinine but, most important, of improving the poor clinical outcomes that have been associated with AKI. This would mean, for example, reducing in-hospital mortality or the need for dialysis. In addition, it is recognized that several remote consequences are associated with AKI, including increased mortality, cardiovascular events, and hospitalization. Moreover, generally it had been accepted that patients who did not die of AKI essentially recovered and had “good” renal outcomes. We now know that in a small subgroup of patients, AKI is associated with a permanent loss of kidney function that may progress to ESRD. Additionally, it is important to recognize that, conceptually, a particular treatment may not affect peak serum creatinine but may have a substantial effect on regeneration and preventing fibrosis, thus resulting in long-term benefit. In summary, treating AKI would imply not just preventing or treating a rise in serum creatinine but preventing or treating many of the immediate and remote clinical consequences associated with AKI.

EMERGING OPTIONS FOR AKI THERAPY

We briefly describe emerging therapies for AKI. In current ongoing clinical trials, AKI develops in predictable clinical settings, including cardiac surgery, administration of contrast agents, and sepsis. We give several examples of these studies and include an additional study in which therapy is administered in a setting requiring dialysis. This list is certainly not all-inclusive but is meant to illustrate that the therapies being developed encompass different points in one pathophysiologic pathway or different pathophysiologic mechanisms.

α-Melanocyte–Stimulating Hormone

The α-melanocyte–stimulating hormone (α-MSH) is a well known melanocortin

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Correspondence: Dr. Sudhir V. Shah, 4301 West Markham Street, Slot 501, Little Rock, AR 72205. Email: shahsudhirv@uams.edu

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agonist that mediates protective roles upon binding to the melanocortin receptor. Several studies have shown that α-MSH has anti-inflammatory and antiapoptotic activities.1,2 Some critical animal studies demonstrated that α-MSH protects from AKI due to ischemia-reperfusion,2 nephrotoxins, and sepsis.3 AP214 is an α-MSH analogue with a 10-fold greater affinity for the melanocortin-1 receptor compared with native MSH that has been developed by Action Pharma and licensed recently by Abbott/AbbVie as ABT-719. In a study using the cecal ligation and puncture animal model of sepsis, Doi et al. showed marked functional and histologic protection against AKI and reduced mortality when AP214 was administered at 0 and 6 hours before surgery and, most interestingly, even when it was administered up to 6 hours after surgery.3 In a phase IIa study, AP214 administered in a dose of 600 μg/kg around the time of cardiac surgery decreased the incidence of AKI.4 In a phase IIb randomized, double-blind, placebo-controlled study for the prevention of AKI in patients undergoing high-risk cardiac surgeries, ABT-719 significantly reduced the composite endpoint consisting of death, need for RRT, or a 25% reduction in renal function during a 90-day postoperative period.5 These longer-term clinical efficacy effects are exceedingly important because, as mentioned earlier, the FDA does not consider the reduction in serum creatinine as an acceptable endpoint for registering a drug in the United States. Also ongoing is a safety and efficacy trial of multiple dosing regimens of ABT719 for the prevention of AKI in patients undergoing high-risk cardiac surgeries (abdominal, vascular, and cardiothoracic) with baseline CKD, diabetes, proteinuria, or history of cardiovascular disease.6

QPI-1002 (15NP): A Small Interfering RNA
Several investigators have documented the importance of p53 activation in renal ischemia-reperfusion and cisplatin nephrotoxicity.7,8 The apoptotic program triggered by p53 depends on its transcriptional activity as well as its direct interaction with the bcl-2 family members at the level of mitochondrial membrane. Quark Pharmaceuticals is a company that focuses on the discovery and development of novel RNAi-based therapeutics that include small interfering RNA (siRNA).9 QPI-1002, also designated as 15NP, is a synthetic siRNA that temporarily inhibits p53 expression in early development. Molitoris and colleagues demonstrated that 15NP is filtered rapidly at the glomerulus and is taken up actively by proximal tubular epithelial cells,10 and that p53 siRNA was effective in a model of ischemia-reperfusion. In dose- and time-optimization studies, siRNA was effective when administered between 16 hours before clamping and 8 hours after clamping, with injections administered at 2 and 4 hours after injury proving the most effective.

15NP is the first siRNA to be systemically administered in humans. Quark has recently completed a multicenter, randomized, double-blind, dose-escalation phase I trial.11 With use of data from animal studies, the intravenous injection in human studies was carried out within 4 hours of bypass surgery, and pharmacokinetic data were obtained during the first 24 hours. Follow-up was conducted for safety and dose-limiting toxicities until hospital discharge and then by phone at 6–12 months after surgery.

Bone Morphogenetic Family of Proteins
Bone morphogenetic proteins, BMPs, are a family of proteins belonging to the TGF-β superfamily that regulate growth, cell differentiation, apoptosis, and tissue repair. BMPs mediate signaling through the Smad pathway. The signaling transduction through BMPs is regulated by BMP antagonists and agonists. THR-184 (Thrasos Innovation, Inc.), an agonist of the BMP pathway, elicits its effect through translocation of the phosphorylated Smad protein in the nucleus.12 Upon phosphorylation, Smads are translocated rapidly to the cell nucleus through their association with Smad4. Preclinical studies have shown BMPs to be protective in AKI12,13; administration of THR-184 significantly reduced serum creatinine levels in an ischemia-reperfusion model and resulted in significant histologic protection. In the control group, epithelial thinning and sloughing, epithelial detachment, and tubular dilatation were frequent and much reduced in the treated group. In phase I, THR-184 demonstrated excellent safety and pharmacokinetic profiles, and the company is recruiting for a phase II multicenter study of patients undergoing cardiac surgery to determine whether THR-184 reduces the frequency, severity, duration, and complication of AKI after cardiac surgery.14

Mesenchymal Stem Cells
The overall rationale for using stem cells is that single-agent therapies usually affect only one or a limited number of various pathways that characterize pathogenesis or organ repair. Mesenchymal stem cells (MSCs) are fibroblast-like cells generated in the bone marrow that can be used to differentiate into osteocytes, chondrocytes, and adipocytes. These cells do not express blood-group antigens or MHC class II antigens, obviating the need for blood or tissue typing. MSCs can be generated readily from small-volume bone marrow aspirate and subsequently can be expanded readily in culture on a large scale, enabling production of a standardized cell product suitable for off-shelf use.

It is now recognized that the number of differentiated stem cells that contribute to an organ’s parenchyma is quite low and that alternative mechanisms, such as paracrine action, are likely to be mediators of tissue protection and regeneration.15 Adult stem cells, particularly MSCs, administered after organ injury exert complex paracrine and endocrine action, including secretion of growth factors and cytokines, modulation of immune response, mitogenics, anti-apoptotic and anti-inflammatory effects, and stimulation of vasculogenesis and angiogenesis. Intracarotid administration of MSCs in a rat model of renal ischemia resulted in significantly improved renal function and a marked improvement in tubular injury, as well as a reduction in the apoptotic score.16
In addition, administration of MSCs considerably improved renal function and histologic findings in AKI models of cisplatin\textsuperscript{17} and glycerol.\textsuperscript{18}

A dose-escalating phase I clinical trial tested the safety and feasibility of MSC in patients at high risk of postoperative AKI. After surgery, AC607 (AlloCure, Inc.) was administered into the suprarenal aorta. This study shows that AC607 was safe and well tolerated in patients undergoing cardiac surgery who are at high risk for AKI. Preliminary analysis indicated potential benefits, although the study was too small to provide any meaningful conclusion. AlloCure is conducting a 200-patient study (ACT-AKI) of patients who have undergone cardiac surgery and have a 0.5-mg/dl rise in serum creatinine within 48 hours of surgery. The primary endpoint is time to kidney recovery, and the secondary endpoint is the composite of incidence of dialysis and mortality.\textsuperscript{19}

**RenalGuard Therapy**

Current guidelines for AKI essentially state that there is no evidence for the utility of diuretics in preventing or treating AKI.\textsuperscript{20} However, evidence does indicate that having high urine output prevents contrast nephropathy, provided that efforts are made to prevent dehydration. RenalGuard therapy (PLC Medical Systems, Inc.) consists of a closed-loop fluid management system by which an automated match of high urine output (obtained by using a loop diuretic) in real time is obtained using a high-volume fluid pump. The Renal Insufficiency after Contrast Administration Trial II, with 146 patients in the control and 146 in the RenalGuard group, both with an eGFR of about 30 ml/min per 1.73 m\textsuperscript{2}, demonstrated that the use of RenalGuard reduced contrast-induced AKI from 25% in the control to 11% in the treatment group.\textsuperscript{21} Many other studies have similar results, and an ongoing United States phase III trial has enrolled approximately 400 patients.\textsuperscript{22}

**Alkaline Phosphatase**

Alkaline phosphatase is an endogenous enzyme that acts by detoxification of proinflammatory substances, such as LPS and extracellular ATP.\textsuperscript{23} Alkaline phosphatase dephosphorylates ATP to produce adenosine, which promotes anti-inflammatory properties and prevents tubular damage. Additionally, dephosphorylated LPS produced by the action of alkaline phosphatase acts as an antagonist for the LPS receptor TLR4 and prevents an inflammatory response and renal damage. Levels of alkaline phosphatase are reduced in several disorders, including AKI. AM-Pharma BV, based in The Netherlands, has conducted clinical trials on intravenous alkaline phosphatase for treatment of AKI. In a phase II randomized controlled trial, infusion of bovine alkaline phosphatase within 48 hours of diagnosis of AKI secondary to sepsis resulted in a significant reduction in the systemic markers C-reactive protein and IL-6, and urinary excretion of kidney injury molecule-1 and IL-18, but not neutrophil gelatinase-associated lipocalin (NGAL).\textsuperscript{23} In addition, endogenous creatinine clearance was significantly higher up to day 28 in the treated group relative to placebo.\textsuperscript{23} RRT requirement decreased, but this did not reach significance. Although these are interesting studies that provide proof of concept that treatment can be initiated as late as 48 hours after diagnosis of AKI, sourcing of purified bovine alkaline phosphatase for widespread therapeutic use may prove to be problematic. Therefore, AM Pharma developed a recombinant human alkaline phosphatase that has demonstrated anti-inflammatory and tissue protective properties in rat models of ischemia-reperfusion–induced and LPS-induced AKI.\textsuperscript{24} Currently, recombinant human alkaline phosphatase is undergoing safety and dose escalation studies (phase I). A placebo-controlled, double-blind, randomized, phase II clinical trial to treat patients diagnosed with sepsis-associated AKI is expected to start in 2014.

**Catalytic Iron**

Critical to the importance of iron in biologic processes is its ability to cycle reversibly between its ferrous and ferric oxidation states. This precise property, which is essential for its functions, also makes it very dangerous because free iron can catalyze the formation of free radicals.\textsuperscript{25} There are two broad lines of evidence for the role of labile iron in disease states: It is increased in these disease states, and iron chelators provide a protective effect, thus establishing a cause-effect relationship. Several studies conducted by different investigators have demonstrated a marked and specific increase in catalytic iron content, as well as its protective effects on renal function and on histologic evidence of renal damage in myoglobinuric, ischemic, and contrast-, gentamicin-, and cisplatin-induced AKI.\textsuperscript{26,27} The discovery of NGAL, which is an important iron-transporting and iron-translocating compound, provides additional evidence for the importance of iron in AKI.\textsuperscript{28} Infusion of NGAL has been demonstrated to protect against renal ischemia-reperfusion injury.\textsuperscript{29}

Several studies in which hepcidin (which helps to sequester iron)\textsuperscript{30} is associated with protection\textsuperscript{31,32} also support the role of catalytic iron in AKI. In a comprehensive and thoughtful analysis of the various novel biomarkers that have been examined after cardiopulmonary bypass--associated AKI, Haase et al. concluded that free iron–related kidney injury appears to be the unifying pathophyslogic connection for these biomarkers.\textsuperscript{31} The availability of iron chelators with favorable adverse-effect profiles for short-term use makes them attractive for clinical trials aimed to prevent or treat AKI.

**Renal Cell Therapy and Bioartificial Renal Epithelial Cell System Therapy**

Current RRTs substitute for solute and volume clearance but do not replace the endocrine and metabolic function. David Humes and colleagues have developed a standard hemofiltration cartridge with human renal tubular cells grown along the inner surface of the hollow fibers.\textsuperscript{33}

The renal tubule assist device (RAD) is incorporated in series with a separate hemofiltration cartridge in an extracorporeal perfusion circuit. A phase II,
multicenter, randomized trial involving 58 patients with AKI and who had re-
quired continuous RRT (CRRT) dem-
onstrated that, at 28 days, the mortality
was 33% in the RAD group and 61% in
the CRRT group.34 The Kaplan–Meier
analysis revealed that survival through
day 180 was significantly improved in
the RAD group, and the Cox propor-
tional hazard model suggested that the
risk for death was approximately 50% of
that observed in the CRRT-alone group.
Tumlin et al. reported substantial im-
provement in patients’ outcomes over
standard-care therapy with the use of a
selective cytophoretic device.35 The pro-
duction and distribution of RAD devices
would be a major obstacle in the wide-
spread adoption of renal cell therapies.
A solution to that problem was the de-
velopment of a cell system that would be
cryopreservable to enable distribution,
storage, and therapeutic use at point-of-
care facilities. The bioartificial renal ep-
ithelial cell system, BREC, was developed
for this intent—a device that functions
as a combined bioreactor, cryostorage de-
vice, and cell therapy device.36

THREE WINDOWS OF OPPORTUNITY

There are three windows of opportunity:
to prevent AKI, to treat AKI after its
onset, and to halt progression to ESRD.
Several important considerations for de-
signing clinical trials in AKI were dis-
cussed during the National Institute of
Diabetes and Digestive and Kidney Dis-
eases (NIDDK) 2-day conference, “Clin-
ical Trials in AKI: Clinical Opportunities
and Barriers,” and have been pub-
lished.37 These articles address the ad-
vantages and challenges of studying
different patient populations and pre-
ventive trials versus treatment trials.
For example, the major advantage of a
preventive trial is that the exact timing of
the insult is known. However, major dis-
advantages include the low incidence
rate, which necessitates a large number
of patients for well designed trials with
adequate power and requiring good es-
timates of the event rate and the realistic
estimates of the effect of intervention.
For example, the Prevention of Serious
Adverse Events following Angiography
trial, known as the PRESERVE trial,
will address the use of N-acetylcysteine
versus placebo and sodium bicarbonate
versus normal saline for the prevention
of contrast-induced AKI in the setting of
coronary and noncoronary angiography.
The PRESERVE trial is notable in that it
plans to enroll 8680 patients with an
eGFR<60 ml/min per 1.73 m² and di-
abetes mellitus or eGFR<45 ml/min per
1.73 m².38

In currently designed clinical studies,
it is generally accepted that there is a very
small therapeutic window. These trials
use a predictable setting, such as cardiac
surgery, where patients can be monitored
and treatment instituted a very short time
after injury. In these studies the event that
triggers inclusion is based on serum creatinine, and, as alluded to previously,
one still has to address the issue of clinical
endpoints rather than changes in serum creatinine. Several recent animal studies
have initiated treatment after the in-
duction of injury and have shown protective
effects, as described in the previous
section. Some of the flaws in clinical trial
design contributing to poor outcomes
and potential strategies for designing
clinical trials for AKI have recently
been reviewed.39 In addition, the Kidney
Research National Dialogue, supported
by NIDDK, has recommended future
opportunities for improving the preven-
tion, diagnosis, and treatment of people
with AKI.40

Perhaps somewhat overlooked and
neglected in subsets of patients with
AKI is the opportunity to halt progres-
sion to ESRD. Several studies from 2008
through 2010 have confirmed that pa-
tients who survive an episode of AKI
have a significant risk for the develop-
ment of advanced CKD.41 In Ishani’s
study, the risk of ESRD was 13 times
higher in patients without a history of
AKI or CKD.42 In a retrospective
study, Wald et al. reported that patients
with AKI requiring dialysis were more
than three times more likely to develop
ESRD than control-matched patients.43
Lo et al. reported that an episode of
dialysis-requiring AKI was associated
with a 28-fold increase in the risk of de-
veloping advanced CKD and a 2-fold in-
crease in mortality.44 The data in this
study indicate that even after renal rec-
covery, severe AKI is often followed by
progression to advanced-stage CKD.

Chawla and Kimmel have estimated
the effect of AKI as a contributor to the
ESRD population.45 We have modified
their assumption somewhat to be even
more conservative. The population inci-
dence of AKI is approximately 2000 per
million of the population. Given the cur-
rent population of the developed world
(United States, Canada, Western Europe,
and Australia) of approximately 1 bil-
lion, there will be 2 million patients de-
veloping AKI, of whom half will survive.
Of these patients, approximately 15%
will advance to CKD within 24 months,
resulting in approximately 150,000–
200,000 cases per year. AKI has thus
come to be a very important contributor
to the ESRD population. Similarly, Hsu
et al. has made some estimates on the
contribution of AKI to ESRD and esti-
imated that perhaps as much as a quarter
of the increase in ESRD between 1988
and 2002 can be attributed to AKI.46
This is attributed to changes in incidence
and outcome of patients with AKI.46 The
increasing incidence of and nonrecovery
from AKI may partly explain why the in-
crease in ESRD incidence has outpaced
growth in CKD prevalence. Thus, any
treatment of AKI must take into account
its contribution toward ESRD.

It is striking that, as opposed to 76% of
the patients with myocardial infarction
who are followed by cardiologists, only
10% of patients with AKI are followed
by nephrologists.45 It is important that se-
lected patients with AKI have a follow-
up with a nephrologist. Currently, four
factors have been identified as risk fac-
tors leading to CKD progression. These
are age, severity of AKI, diabetes, and
low serum albumin. It would be ex-
tremely helpful if robust biomarkers ex-
isted to identify patients with AKI who
are likely to have progressive kidney dis-
ease. An ongoing National Institutes of
Health–funded study, the Assessment,
Serial Evaluation, and Subsequent
Sequelae of Acute Kidney Injury,47 is examining how a hospital episode of AKI independently affects risk for chronic disease development and progression, cardiovascular events, death, and other important patient-centered outcomes. This study consists of 1100 adults and a pediatric population and will evaluate, among other things, the utility of novel blood and urine biomarkers that could be used for clinical trials to improve outcomes after AKI. Most important would be identification of clinical characteristics and biomarkers of patients who are likely to have progressive kidney disease leading to ESRD.

PATHWAYS TO ACCELERATE A CURE FOR AKI

The pharmaceutical industry spends significant sums of money on clinical trials conducted in the cardiovascular space, yet is reluctant (recent exception being Abbott/AbbVie) to enter the kidney market. Groups from other specialties have successfully canvassed “Big Pharma” and engaged them to develop drugs by demonstrating an interested and active community and pointing out the commercial aspects. Meanwhile, a few relatively small pharmaceutical companies are making serious attempts at preventing and treating AKI. We as an interested community should make the task easier: For example, thought leaders with no financial interest could initiate a dialogue with the FDA regarding acceptable endpoints that are within the goal of a realistic trial. Organizations such as the Parkinson's Action Network and Diabetic Retinopathy Clinical Research Network have done this successfully. On the basis of a careful natural history in untreated groups of clinical trials and epidemiologic studies, surrogate markers linked to clinical outcomes can be determined. New treatments can then be evaluated using these surrogates, making it possible to evaluate novel treatments.

Also needed is an AKI network modeled after the Acute Respiratory Distress Syndrome Network, a multicenter network initiated by the National Heart, Lung, and Blood Institute that tests promising agents or strategies, especially if they are unlikely to be studied by industry. The trials are designed to be of sufficient size and importance to change practice. Such a network could also be used by smaller pharmaceutical companies interested in evaluating novel therapies.

Currently, organizations such as the American Society of Nephrology raise funds to be used primarily for research purposes, and the National Kidney Foundation raises funds targeted toward patient care. These organizations, which have an interest in curing kidney disease, should consider adopting a model sometimes referred to as "catalytic philanthropy."48 In such a model the donor, rather than passively make gifts to charitable organizations, plays an active role toward achieving a specific goal. The model that we propose is a variation of this theme, whereby money is raised from donors and then directed toward the specific goal of evaluating novel treatments for kidney disease, especially agents that are unlikely to be tested by the pharmaceutical industry because of lack of patents or patent expiration.

Finally, Dr. George E. Schreiner, who died recently, was instrumental in getting ESRD care covered by Medicare in 1972. Today Medicare spends almost $33 billion annually on ESRD.49 Professional and patient-centered organizations should make an attempt to convince government that a small percentage of this expenditure be spent specifically toward therapies to prevent and treat AKI and halt progression to CKD, which would result in improved patient care and enormous savings long term.

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6. ClinicalTrials.gov: A safety and efficacy trial of multiple dosing regimens of ABT-719 for


