AJKD
In Translation

Alkaline Phosphatase: A Possible Treatment for Sepsis-Associated Acute Kidney Injury in Critically Ill Patients

Esther Peters, MSc,[1,2] Suzanne Heemskerk, PhD,[1,2] Rosalinde Masereeuw, PhD,[2] and Peter Pickkers, MD, PhD[1]

Acute kidney injury (AKI) is a common disease in the intensive care unit and accounts for high morbidity and mortality. Sepsis, the predominant cause of AKI in this setting, involves a complex pathogenesis in which renal inflammation and hypoxia are believed to play an important role. A new therapy should be aimed at targeting both these processes, and the enzyme alkaline phosphatase, with its dual mode of action, might be a promising candidate. First, alkaline phosphatase is able to reduce inflammation through dephosphorylation and thereby detoxification of endotoxin (lipopolysaccharide), which is an important mediator of sepsis. Second, adenosine triphosphate, released during cellular stress caused by inflammation and hypoxia, has detrimental effects but can be converted by alkaline phosphatase into adenosine with anti-inflammatory and tissue-protective effects. These postulated beneficial effects of alkaline phosphatase have been confirmed in animal experiments and two phase 2a clinical trials showing that kidney function improved in critically ill patients with sepsis-associated AKI. Because renal inflammation and hypoxia also are observed commonly in AKI induced by other causes, it would be of interest to investigate the therapeutic effect of alkaline phosphatase in these nephropathies as well.
Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Acute kidney injury; alkaline phosphatase; biopharmaceutical; adenosine; sepsis; hypoxia; renal inflammation; renal failure; systemic inflammation.

BACKGROUND

The incidence of acute kidney injury (AKI) in the intensive care unit (ICU) is estimated to be around 20%-50% and contributes to mortality of >50%.[1] Moreover, up to one-third of all critically ill patients surviving an episode of AKI develop chronic kidney disease, accompanied by an enormous financial burden on society.[2] The pathogenesis of AKI is very complex, but >30% of the cases are caused by sepsis.[3] Unfortunately, no pharmacologic interventions currently exist to treat AKI, with only supportive care such as renal replacement therapy (RRT) available. Therefore, an urgent need for new treatment options exists. A promising novel treatment strategy is the enzyme alkaline phosphatase (ALP; also referred to as AP). Originally, ALP was developed as an anti-inflammatory sepsis therapy; however, the enzyme appeared to be predominantly renal protective in an ICU subpopulation of patients with sepsis-associated AKI.[4,5] In this review, we discuss the pathogenesis of sepsis-associated AKI and elaborate on ALP as a possible treatment strategy.

CASE VIGNETTE

A 72-year-old man admitted to the hospital with abdominal pain was suspected to have intestinal ischemia or a ruptured abdominal aneurysm. Antibiotic treatment was started and laparotomy was performed, which revealed intestinal perforation and fecal leakage due to a rectosigmoid mass. Postoperatively, the patient was transferred to the ICU, where antibiotic treatment was continued. Upon admission to the ICU, his blood pressure dropped despite fluid resuscitation (mean arterial pressure < 70 mm Hg), and vasopressor therapy was started. Leukopenia was present (white blood cell count $< 2 \times 10^3/\mu L$). One day later, respiratory insufficiency developed, ventilatory support was initiated, and blood cultures grew Gram-negative rods. The following day, urine flow decreased to <0.5 mL/kg/h, and the patient's serum creatinine level increased from 1.14 mg/dL (101 μmol/L; corresponding to creatinine clearance [CCr] by the Cockcroft-Gault equation of 83 mL/min) to 1.44 mg/dL (128 μmol/L; CCr, 65 mL/min).[6]

The patient fulfilled the criteria of a phase 2a clinical trial of ALP[5] and was enrolled in the study. Upon deblinding at the end of the trial, it was revealed that he had been randomly assigned to the group receiving ALP. During the 24 hours prior to ALP administration, his urine flow was 0.5 ± 0.1 mL/kg/h, but for the 48 hours following drug treatment, it increased to 0.7 ± 0.3 mL/kg/h. Simultaneously, his creatinine level decreased to 1.29 mg/dL (114 μmol/L; CCr, 106 mL/min). The following day, the patient underwent a second laparotomy and proceeded to recover quickly. While the clinical course was complicated by a wound dehiscence for which additional surgery was required and an episode of delirium, kidney function improved over the next days as his creatinine level decreased to

From the [1]Department of Intensive Care Medicine, Nijmegen Institute for Infection, Inflammation and Immunity, and [2]Department of Pharmacology and Toxicology, Nijmegen Centre for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands.

Received August 3, 2013. Accepted in revised form November 18, 2013.

Address correspondence to Peter Pickkers, MD, PhD, Department of Intensive Care Medicine, Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Medical Center, PO Box 9101, Internal Mailbox 710, 6500 HB Nijmegen, the Netherlands. E-mail: peter.pickkers@radboudumc.nl

0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2013.11.027

0.95 mg/dL (84 μmol/L; CCr, 100 mL/min) and urine flow increased to 1.4 ± 0.7 mL/kg/h. The patient was extubated on day 7 and discharged from the ICU the following day. During study follow-up at day 28, serum creatinine level decreased further to 0.61 mg/dL (54 μmol/L; CCr, 155 mL/min).

PATHOGENESIS

The pathogenesis of sepsis-associated AKI is far from completely understood due to its complexity and multifactorial origin and because of the lack of kidney biopsies from this vulnerable patient population. The concept of reduced renal blood flow as a sole contributor to sepsis-associated AKI currently is questioned because several studies of animals and of humans have shown that sepsis-associated AKI develops during normal or even increased renal blood flow.[7] These findings introduce a paradigm shift, suggesting an important role for inflammation, altered renal microcirculation, and possibly unbalanced renal bioenergetics (Fig 1).[8]

Inflammatory Response

During sepsis, the body's response to an infection is characterized by the release of several detrimental inflammatory mediators, including many proinflammatory cytokines and arachidonic acid metabolites; upregulation of inducible nitric oxide (NO) synthase (iNOS); and activation of the complement cascade.[9] Another harmful mediator is extracellular adenosine triphosphate (ATP), which is released during cell stress and stimulates inflammation and tissue injury by attracting phagocytes and activating the NLRP3 inflammasome.[10,11] Sepsis can be caused by different pathogens, and certain motifs of these pathogens, known as pathogen-associated molecular patterns, are recognized by the innate immune system. These pathogen-associated molecular patterns signal by Toll-like receptors (TLRs) or other pathogen recognition receptors, thereby triggering an inflammatory response.[12]

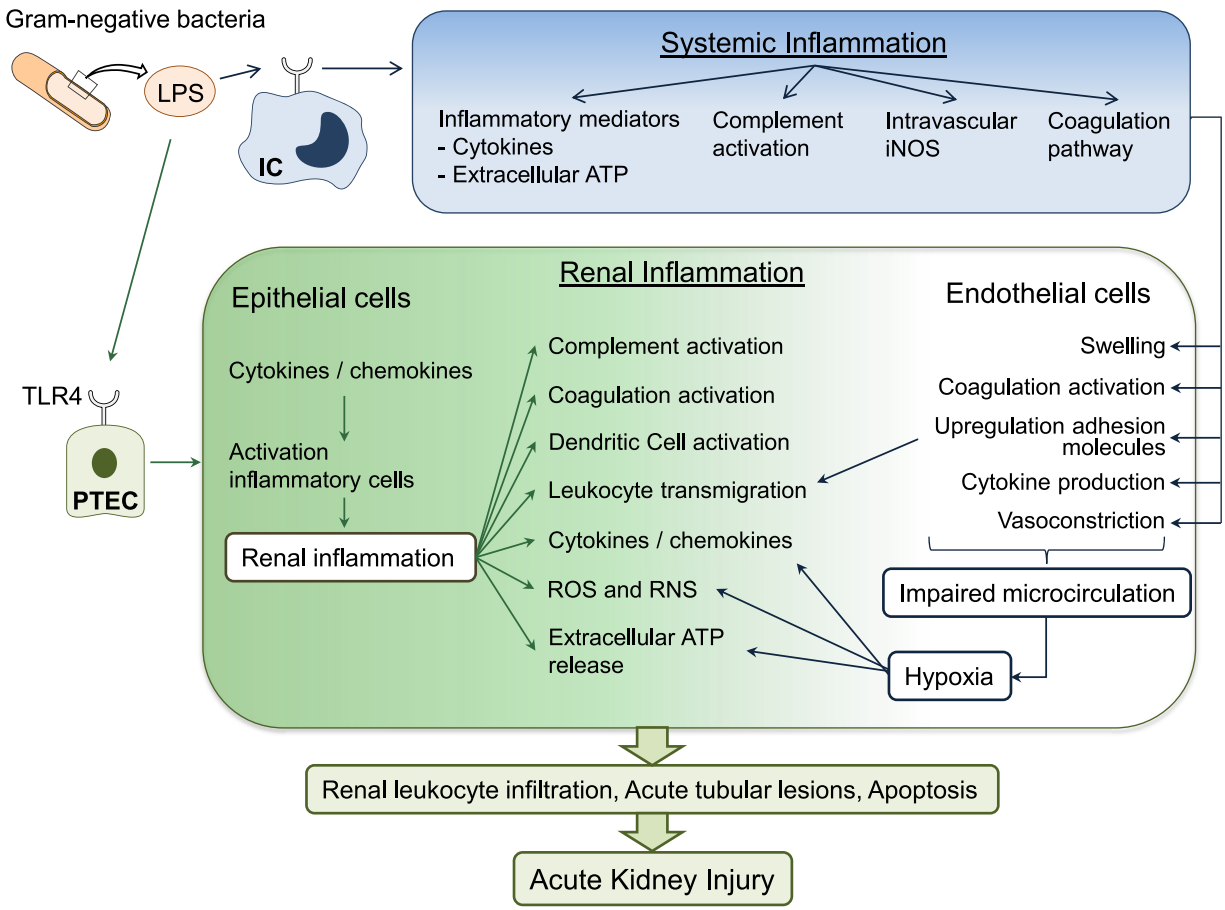

Figure 1. Renal inflammation and impaired microcirculation in the pathogenesis of sepsis-associated acute kidney injury (AKI). Lipopolysaccharide (LPS) binds to Toll-like receptor 4 (TLR4) on immune cells (ICs), triggering the inflammatory response causing systemic inflammation. Alternatively, LPS binds to TLR4 expressed on proximal tubule epithelial cells (PTECs), inducing renal inflammation. Endothelial cells exposed to LPS and circulating cytokines may result in impaired renal microcirculation, causing hypoxia. The immune response is enhanced further by renal inflammation and hypoxia, eventually causing AKI characterized by leukocyte infiltration, acute tubular lesions, and apoptosis. Abbreviations: ATP, adenosine triphosphate; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; RNS, reactive nitrogen species.