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WHAT'S NEW IN INTENSIVE CARE

New drugs for acute kidney injury

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Acute kidney injury (AKI) is common in critically ill patients and is associated with serious short and long-term complications, including chronic dialysis dependence, and increased mortality [1]. There is no approved pharmacological therapy to prevent, treat or enhance recovery from AKI. Current strategies focus predominantly on preventing further deterioration of renal function [2, 3].

Challenges in determining the exact timing, etiology, and phase of AKI may account for the limited progress in this field. The use of additional biomarkers to define AKI may provide granularity enabling earlier detection [4, 5]. Nevertheless, research addressing the pathophysiology of AKI has identified potential therapeutic targets, including pathways involved in hemodynamics and oxygen delivery, inflammation, cellular metabolism and oxidative stress, apoptosis, and cellular repair and fibrosis [6]. In future, identification of different AKI sub-phenotypes, informed by emerging time-sensitive and AKI phase-specific biomarkers, may aid accelerated and successful drug development in this critical area of unmet need. Here, we describe selected compounds that impact known pathophysiological processes and have been studied in humans (Fig. 1).

Hemodynamics and oxygen delivery

Angiotensin 2 (AngII), an endogenous vasoconstrictor, preferentially constricts the glomerular efferent arteriole, thus increasing glomerular filtration rate. A post-hoc analysis of the ATHOS-3 randomized controlled trial (RCT) showed that patients with vasodilatory shock on renal replacement therapy (RRT) discontinued RRT earlier (38% vs 15% by day 7, $p=0.007$) and had a lower 28-day mortality (30% vs 53%, $p=0.012$) if randomized to AngII compared to placebo [7]. Confirmation is sought in the ASK-IT trial (NCT00711789). Small trials suggested that vasopressin might improve renal function, however, vasopressin and also the selective vasopressin V1a receptor agonist selepressin did not show a difference in the need for renal replacement therapy compared to norepinephrine in larger trials [8]. The putative nephroprotective effects of levosimendan, an inodilator, may be mediated by improved cardiac function, or by glomerular afferent arteriolar vasodilation. A meta-analysis of 13 trials in cardiac surgery patients showed that levosimendan reduced the incidence of postoperative AKI [odds ratio (OR) 0.51, 95% confidence interval (CI) 0.34–0.76; $p=0.001$] and use of RRT (OR 0.43; 95% CI 0.25–0.76, $p=0.002$) [9]. Further results are awaited [e.g. the LEVOAKI trial (NCT02531724)]. In patients requiring vasopressor support, the optimal blood pressure target is unknown. Whilst a higher blood pressure target was associated with less RRT use in septic shock patients with known hypertension (32% vs 42%, $p=0.046$), there was no difference in mortality [8].

Inflammation

AKI is an inflammatory syndrome. Multiple anti-inflammatory interventions have been tested in different patient cohorts. Reltecimod, a CD28 T-lymphocyte receptor mimetic that inhibits T-cell responses, improved renal function in a phase 2 trial [10], but did not significantly improve resolution of organ dysfunction in the intention to treat cohort of a phase 3 RCT in patients with sepsis from necrotizing soft tissue infections [11]. Two large RCTs and a subsequent meta-analysis concluded that steroids did not reduce the risk of AKI post-operatively [12]. However, in a post-hoc analysis, dexamethasone was associated with reduced need for RRT (relative risk, 0.44; 95% CI 0.19–0.96), especially in patients with advanced

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chronic kidney disease [13]. Further research is necessary to confirm these findings.

Alkaline phosphatase, an endogenous detoxifying enzyme, dephosphorylates pathogen- and damage-associated molecular patterns. A phase 2 trial in patients with sepsis-associated AKI showed that recombinant alkaline phosphatase did not significantly improve short-term renal function, but significantly improved longer-term renal function and almost halved mortality (14 vs 27%, $p=0.02$) [14]. A phase 3 RCT (REVIVAL) in patients with sepsis-associated AKI with a primary endpoint of 28-day mortality is ongoing (NCT04411472).

Cellular metabolism and oxidative stress

Nicotinamide adenine dinucleotide (NAD) is essential for energy generation and cell health. Sirtuins are NAD-dependent enzymes involved in cellular energy metabolism and maintaining undamaged deoxyribonucleic acid (DNA). Preclinical data shows that the sirtuin SIRT1 is protective against kidney damage resulting from oxidative injury. The activity of SIRT1 can be augmented by NAD + precursors. A single-center phase 2 RCT in cardiac surgery patients is ongoing to evaluate the efficacy of NAD supplementation (NCT04342975).

Apoptosis

The tumor suppressor protein, coined P53, is involved in apoptosis, cell cycle regulation and angiogenesis, which all contribute to the pathogenesis of AKI. A small interfering ribonucleic acid (siRNA), QPI-1002 (teprasiran), inhibits P53, and demonstrated a significant 13% absolute risk reduction (OR 0.58, 95% CI 0.37–0.92, $p=0.02$) in AKI incidence in a phase 2 trial in cardiac surgery patients [15], in addition to promising phase 2 results for the prevention of delayed graft function following kidney transplantation (NCT00802347). However, a subsequent phase 3 trials in cardiac surgery (NCT03510897), as well as in kidney transplant patients (NCT02610296) were reportedly negative.

Cellular repair and fibrosis

A variety of agents have been developed targeting pathways that promote renal tubular repair and regeneration in AKI, thus decreasing fibrosis and promoting recovery. Preclinical AKI studies demonstrated several benefits with mesenchymal stem cell (MSC) therapy, including anti-inflammatory, antiapoptotic, antioxidative, antifibrotic, immunomodulatory and proangiogenic effects; all promoting accelerated recovery [16]. However, a phase 2 RCT in cardiac surgery patients showed that

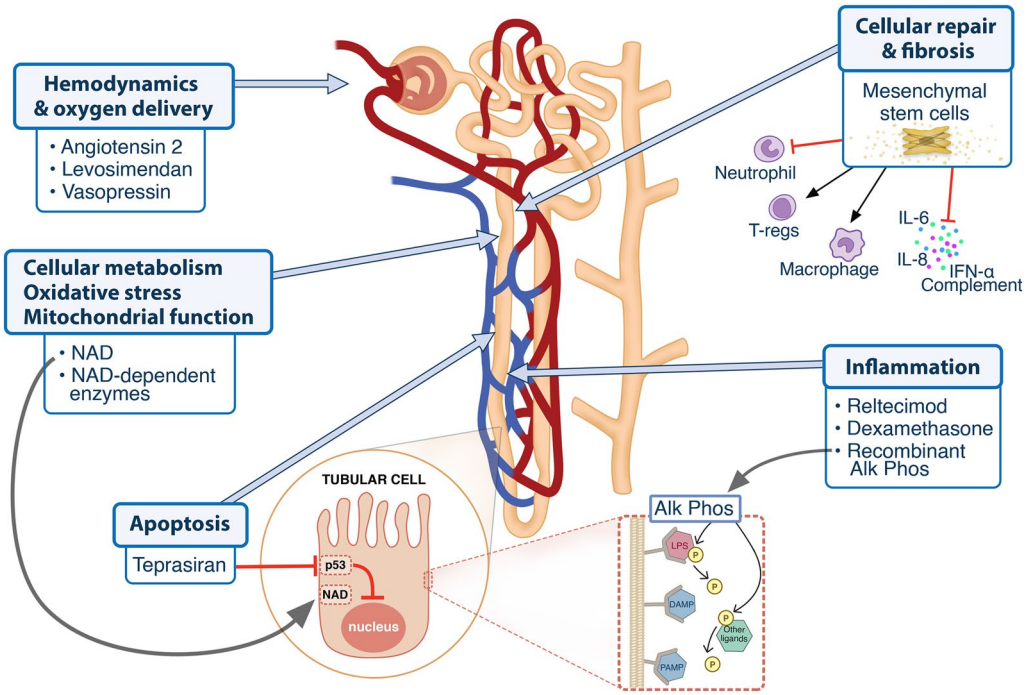

Fig. 1: Selected compounds that impact known pathophysiological processes and have been studied in humans. *Alk Phos* alkaline phosphatase; *DAMP* danger associated molecular pattern; *IL* interleukin; *IFN-α* interferon alpha; *LPS* lipopolysaccharide; *NAD* Nicotinamide adenine dinucleotide; *T-regs* regulatory T-cells; *PAMP* pathogen associated molecular pattern

administration of allogeneic MSCs did not decrease the time to recovery of kidney function [17].

The bone morphogenic protein-7 agonist THR-184 has anti-inflammatory, anti-fibrotic, anti-apoptotic and tubular regenerative effects, but failed to prevent or ameliorate AKI following cardiac surgery [18]. More recently, hepatocyte growth factor (HGF; ANG-3777) was evaluated in clinical trials post-kidney transplantation (phase 3; NCT02474667) and during cardiac surgery (phase 2; NCT02771509). Both trials have ceased recruitment, but results have not been published. Development plans for both indications are under review in light of reportedly negative primary endpoints in both trials (www.angion.com). Taken together, broad-based cellular therapies and specific targeted pro-regenerative or anti-fibrotic therapies failed to decrease the incidence or severity of AKI.

Take-home message

AKI represents a major burden for both the patient and society, but a dedicated treatment is lacking so far, likely related to its multifactorial nature and our current inability to identify AKI-phenotypes. Nevertheless, with the recent advances in the understanding of its pathogenesis and progress in trial design, a spectrum of targeted therapeutic interventions is emerging that have potential to impact the prognosis of patients with AKI.

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Declarations

Conflicts of interest
PP received speaker honoraria from Baxter and advisory board consulting reimbursement from AM-Pharma, EBI, Sphingotec, Adrenomed, 4Teen4. PM received Trial Steering Committee consultancy payments from AM-Pharma. Other consultancy payments: FAST Biomedical, Novartis, Renibus Therapeutics. MO received speaker honoraria from Fresenius Medical Care, Biomerieux, Baxter and Gilead, and research funding from Fresenius Medical Care, Biomerieux, Baxter and LaJolla Pharma and advisory board consultancy reimbursements from AM-Pharma.

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