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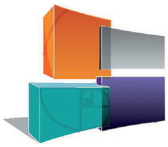

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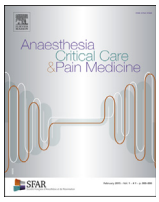

Editorial

A cure for septic AKI: Why not keep the dream alive?

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Acute kidney injury (AKI) is common in patients admitted to the intensive care unit (ICU) and is associated with high mortality and morbidity [1]. Sepsis is the leading cause for AKI in this context and accounts for more than 40% of the cases [1]. Although not entirely understood, septic AKI appears to have a distinct pathophysiology involving damage-associated-molecular-patterns (DAMPS) and pathogens-associated-molecular-patterns (PAMPS) filtration and their interaction with tubular epithelial cells [2]. In addition, inducible nitric oxide synthase (iNOS) upregulation and NADPH activation are believed to lead to an inflammatory cascade resulting in glycocalyx damage, increased capillary permeability, and compromised capillary flow [3,4]. Unfortunately, our understanding of septic AKI pathophysiology remains incomplete and, more importantly, has so far failed to translate into outcome modifying intervention [5].

The body of work by Pickkers and his team has recently generated great hopes. Indeed, it has suggested that alkaline phosphatase (AP), a dephosphorylating enzyme, might have renoprotective effects in sepsis. In a rat model, recombinant AP (recAP) administration was able to prevent LPS-induced increase in proximal tubular injury marker and improve renal function [6]. It was associated with attenuated immunostaining of inflammatory, tubular injury and pro-apoptosis markers [7]. These effects appear to be mediated by inflammatory cascade interruption through lipopolysaccharide (LPS) and extra-cellular ATP and ADP dephosphorylation [6,8]. The same group conducted a pilot randomised controlled clinical trial in 36 adult patients with systemic inflammatory response syndrome (SIRS) and AKI [9]. In this trial, bovine AP administration during 24 hours appeared to be well tolerated and was associated with an improved recovery of endogenous creatinine clearance (ECC). In addition, AP administration was associated with pronounced reduction in systemic markers of inflammation.

In this context, the STOP-AKI trial, an international, adaptive phase 2a/2b randomised double-blind placebo-controlled trial, was conducted [10]. It aimed at evaluating the effect of recAP in critically ill patients with septic AKI on renal function as evaluated by the area under the time-corrected curve for creatinine clearance (ECC) from day 1 to day 7 (AUC_{1-7}). In a first, dose-finding part, eligible patients were randomised to either receive 0.4 ($n = 31$), 0.8 ($n = 32$) or 1.6 mg/kg ($n = 29$) of recAP. Interim analyses suggested that 1.6 mg/kg was the best dosing regimen. Hence, in a second part, patients were randomised to either receive recAP (1.6 mg/kg, $n = 82$) or placebo ($n = 86$). Altogether, 301 patients were included in the trial. Unfortunately, the trial failed to demonstrate a statistically significant difference in its primary outcome: the AUC_{1-7} was 55.1 mL/min (IQR 15.0 to 93.9) in the recAP group versus 45.6 (IQR 17.7 to 112.4) mL/min in the placebo group (absolute difference 9.5 mL/min; $P = 0.47$). The authors adequately concluded that recAP compared with placebo did not significantly improve short-term kidney function.

At first glance, the STOP-AKI trial might just appear as another "negative randomised controlled trial in ICU" or another "major disappointment following exciting pre-clinical and preliminary clinical data". The busy reader might conclude that alkaline phosphatase should be given-up and prompt researchers to return to their bench. Admittedly, this trial does not provide evidence supporting clinical utilisation of recAP outside clinical trials. However, by taking a closer look at the STOP-AKI design and results, numerous elements of hope can be found and enable us to keep the dream alive.

First, the choice of the primary outcome is associated with limitations. In the STOP-AKI trial, authors have selected the area under the curve for ECC between day one and day seven as a primary outcome. This uncommon measure is meant to represent an evaluation of renal function following the intervention. Its interpretation, however, might be difficult. Indeed, serum creatinine (on which calculation of creatinine clearance is based), although commonly used in clinical practice, is known to be a delayed biomarker of renal function and to be subject to dilution [11,12]. It remains however commonly used in clinical practice in the absence of an ideal biomarker of kidney damage. However, given the potential for a delayed effect, the choice of using a seven days window to compare the two groups appears questionable. As discussed below, the choice of a longer time period might have lead to different results. Perhaps, more sensitive biomarkers such as cystatin C or insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinase-2 should have been utilised even if their ability to detect renal recovery has not been clearly established [13,14]. Unfortunately, these biomarkers were not measured in the trial.

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Second, many secondary outcomes point toward potential efficacy. The STOP-AKI data does not exclude a delayed effect of recAP on renal recovery. On the contrary, recAP was associated with a statistically significant improvement in ECC up to day 28 (mean difference on day 28: 18.5 mL/min, $P = 0.006$). Similarly, post hoc mixed effect regression analyses demonstrated a mean difference of 27.6 mL/min (95% CI 8.7 to 38.9, $P = 0.004$) in favor of the recAP group. Hence, the seven days timeframe chosen as a primary outcome might have been too short to capture a beneficial effect of the medication. Then, recAP administration was associated with a lower mortality. This association remained after correction for confounders in multivariable analysis (HR 0.47, 95% CI 0.25 to 0.88, $P = 0.02$). In addition, the reported association seems to have some form of dose dependence further suggesting causality in this association. Obviously, both day 28 renal recovery and mortality were secondary outcomes and, in a methodologically sound analysis, can only be interpreted as hypothesis generating. However, their relevance makes them really hard to ignore. Hence, this "negative" trial contains signal on secondary outcomes suggesting a benefit from reCAP on two important patient centred clinical outcomes. This should strongly prompt for the conduction of trials adequately powered to evaluate such outcomes.

Third, absence of efficacy on the primary outcome might in part be explained by some characteristics of the included population. Indeed, compared with patients enrolled in the pilot trial in which the intervention was associated with efficacy [9], patients enrolled in the STOP-AKI trial presented a lower creatinine clearance at time of randomisation STOP-AKI: 25 (AP) and 37.5 mL/min (placebo) versus Pilot: 50 (AP) and 40 mL/min (placebo) [9]. Application of an intervention in patients with lower AKI stage could logically be expected to be associated with greater chances of reversing the underlying issue. In other words, more severe forms of AKI might be less amenable to recovery and exhibit lower response to the intervention. Perhaps, instead of including patients with overt AKI according to the KDIGO classification, the trial should have used a biomarker-guided initiation of the therapy to identify patients with subclinical AKI. In addition, patients included in the STOP-AKI trial had much more limited inflammatory response as compared with those included in the pilot trial ($>$ 20 fold lower mean levels of Interleukin-6 and lipopolysaccharide biding protein (LBP)). The relevance of this difference remains to be determined.

In conclusion, despite a well-conducted randomised controlled trial leading to a negative primary outcome, recAP remains an exciting drug with the potential to improve renal recovery in critically ill patients with sepsis. Further studies are required to evaluate its effect on delayed renal function and mortality. Such studies might elect to use recent biomarkers of renal injury as part of their inclusion criteria. In the meantime, we can continue to dream of a disease modifying drug for AKI!

Disclosure of interest

TM has no conflict of interest to declare.

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