ALKALINE PHOSPHATASE IMPROVES KIDNEY FUNCTION IN ICU PATIENTS WITH SEPSIS-INDUCED ACUTE KIDNEY INJURY

On behalf of the APREN-study group,

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No conflicts of interest to declare
AKI is large unmet medical need

Acute kidney injury incidence in the Western world is 2 MM patients / year*
~ 700,000 deaths associated with AKI each year

- No drugs licensed to treat AKI
- Current ICU treatment: dialysis

Major causes of Acute Kidney Injury

- **Drug & Contrast Toxins**
  - AKI incidence 1-7%
  - AKI mortality 20-50%

- **Sepsis**
  - AKI incidence 20-60%
  - AKI mortality 30-50%

- **Cardiovascular Surgery**
  - AKI incidence 3-12%, as high as 25% for CHF
  - AKI mortality 20-45%

- **Other**
  - a/o hemorrhage, trauma

* estimate based on literature review, a/o Xue et al, ASN 2006
Alkaline Phosphatase
AKI - AP depletion in damaged renal cortex

*AP levels are depleted in Acute Kidney Injury*

First Phase-II Study in AKI with bovine AP

APSEEP Phase-II (2007)

• 36 patient randomized double-blind prospective sepsis study (2:1)
• 16 patients with Acute Kidney Injury were analyzed as a sub-group
• 24 hrs bovine AP-treatment (iv)
• 28 day follow up

Aged 18-80 yrs
Proven or suspected Gram-negative infection
2 out of 4 SIRS criteria (<24 hrs)
Acute onset of end-organ dysfunction (<12 hrs)

Trial sponsor
AM-Pharma, Bunnik, The Netherlands.

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www.am-pharma.com
Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients*

Suzanne Heemskerk, PhD; Rosalinde Masereeuw, PhD; Olof Moesker; Martijn P. W. J. M. Bouw; Johannes G. van der Hoeven, MD, PhD; Wilbert H. M. Peters, PhD; Frans G. M. Russel, PhD; Peter Pickkers, MD, PhD; on behalf of the APSEP Study Group

Heemskerk, Pickkers, et al. CCM.

**Graph 1:**
- iNOS expression (relative Xn value)
- Baseline 0-24 h
- AP
- Placebo

**Graph 2:**
- Cumulative NO metabolites excretion
- Cumulative NO metabolites excretion (µmol/10 mmol creatinine)
- Day 1: 54 ml/min
- Day 2: 76 ml/min

**Creatinine-clearance (median):**
- AP: 54 ml/min
- Placebo: 80 ml/min
**APSEP Phase-II (2007) Results**

*AP-treatment improves kidney function in patients with AKI and prevents AKI occurrence*

36 sepsis pts

16 AKI pts @ baseline

20 non-AKI pts @ baseline

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**Reduced Dialysis Requirement**

- Placebo: 80% (4/5)
- AP: 36% (4/11)

**AKI occurrence after start of study**

- Placebo: 66% (4/6)
- AP: 29% (4/14)

Bolus 67.5 U/kg, maintenance 132.5 U/kg during 24 hrs.

Mice

![Graph showing survival percentage over time for E. Coli and E. Coli + CIAP.]
Second Phase-II Study in AKI with bovine AP

APREN Phase-II (2010)

- 36 patients prospective randomized placebo-controlled double-blind sepsis-AKI study (1:1)
- Patients had Acute Kidney Injury caused by sepsis
- 48 hrs bovine AP-treatment (iv)
- 28 day follow up

Aged 18-80 yrs
Proven or suspected Gram-negative infection
2 out of 4 SIRS criteria
Evidence for kidney injury
APREN Phase-II Design

- Kidney injury in the absence of underlying primary renal disease:

  \[
  \leq 48 \text{ hrs: } \uparrow \text{ serum creatinine } \geq 150 \text{ } \text{mol/L}
  \]

  \[
  \geq \text{ stage 1 Kidney Injury according to AKIN creatinine criteria:}
  \leq 48 \text{ hrs } \uparrow \text{ serum creatinine } \geq 26.2 \text{ } \mu\text{mol/L or } \geq 1.5 \text{ } \text{–fold}
  \]

  \[
  \geq \text{ stage1 Kidney Injury according to AKIN urine output criteria:}
  \leq 0.5 \text{ ml/kg/h for } \geq 6 \text{h and following adequate fluid resuscitation}
  \]
APREN Phase-II Design

- AP treatment with 67.5 U/kg loading dose and 132.5 U/kg continuous infusion for 48 hours
- Patients on dialysis excluded
- Start dialysis according to ADQI criteria (oliguria+azotemia, anuria+azotemia, hyperkalemia, acidosis, hyponatremia and/or fluid overload)
- Primary endpoint: kidney function improvement, measured by the combined end-point: recovery of creatinine clearance and dialysis requirement (incidence and duration)
Exclusion Criteria

• Pregnant women or nursing mothers and fecund females not on effective contraception.
• Known HIV (sero-positive) patients.
• Patients already on RRT at entry.
• Patients receiving immunosuppressant therapy or on chronic high doses of steroids equivalent to prednisone 1mg/kg/day.
• Patients expected to have rapidly fatal disease within 24 hours.
• Known confirmed gram-positive sepsis.
• Known confirmed fungal sepsis.
• Acute pancreatitis with no established source of infection.
• Any previous administration of exogenous AP.
• Participation in another investigational study within 90 days.
• Patients not expected to survive for 28 days due to other medical conditions such as end-stage neoplasm.
• Known allergy to dairy products including cow milk.
• Sepsis without renal failure as defined in Entry Criteria.
• History of chronic renal failure or history of persistent creatinine level equal or greater than 150µmol/L (1.70mg/dL) prior to entry for reasons other than the current sepsis condition.
Results
## APREN Study Baseline Demographics

<table>
<thead>
<tr>
<th>BASELINE PARAMETER</th>
<th>AP (n=16)</th>
<th>Placebo (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: n (%)</td>
<td>13 (81)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>Age: mean years (SD)</td>
<td>65 (12)</td>
<td>67 (15)</td>
</tr>
<tr>
<td>Height: mean cm (SD)</td>
<td>176 (10)</td>
<td>174 (8)</td>
</tr>
<tr>
<td>Weight: mean kg (SD)</td>
<td>86 (12)</td>
<td>80 (14)</td>
</tr>
<tr>
<td>Temperature &lt;37°C: mean °C (SD)</td>
<td>36.1 (0.8)</td>
<td>36.0 (0.7)</td>
</tr>
<tr>
<td>Temperature &gt;37°C: mean °C (SD)</td>
<td>38.3 (0.8)</td>
<td>38.0 (0.7)</td>
</tr>
<tr>
<td>Heart rate: mean bpm (SD)</td>
<td>103 (23)</td>
<td>105 (22)</td>
</tr>
<tr>
<td>Systolic BP: mean mmHg (SD)</td>
<td>103 (26)</td>
<td>110 (26)</td>
</tr>
<tr>
<td>Diastolic BP: mean mmHg (SD)</td>
<td>52 (13)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>APACHE-II score: mean (SD)</td>
<td>24 (7)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>SOFA score: mean (SD)</td>
<td>10 (4)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Creatinine clearance: mean mL/min (SD)</td>
<td>49.6 (27)</td>
<td>40.0 (37)</td>
</tr>
</tbody>
</table>
AP Treatment Increases Renal Creatinine Clearance

Creatinine clearance is restored to normal in the AP-group within 7 days and remains impaired in the placebo group

\[ P = 0.02 \]
AP-treatment improved creatinine clearance is sustained during study period

* P<0.02 two-way ANOVA repeated measures
AP treatment reduces dialysis requirement

*AP-treatment reduces need for dialysis and relative dialysis duration*

**Dialysis Requirement (ITT)**
Yes/no dialysis requirement during 28 days

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% RRT Incidence</td>
<td>37%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>P=0.28</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AP treatment reduces overall duration of dialysis requirement

Combined end-point (creatinine clearance, dialysis requirement, duration): $P=0.02$
## Exploratory analyses

<table>
<thead>
<tr>
<th>Combined renal parameters (primary variable) *</th>
<th>p = 0.020</th>
</tr>
</thead>
<tbody>
<tr>
<td>eCrCl + RRT requirement + RRT duration</td>
<td>0.020</td>
</tr>
</tbody>
</table>

### Exploratory analyses of other combinations of renal parameters *

<table>
<thead>
<tr>
<th>Combination</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRT requirement + RRT relative duration + eCrCl + AUC serum creatinine</td>
<td>0.005</td>
</tr>
<tr>
<td>RRT requirement + RRT relative duration + eCrCl</td>
<td>0.018</td>
</tr>
<tr>
<td>RRT total duration + eCrCl + AUC serum creatinine</td>
<td>0.001</td>
</tr>
<tr>
<td>RRT total duration + eCrCl</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Secondary end points
Urinary excretion of markers of tubular damage
Markers of inflammation

A

- Treatment
- Placebo
- AP

LBP (ng/mL)

Time (hrs)

0 24 48 72 96 120 144 168

B

- Treatment

IL-6 (pg/mL)

Time (hrs)

0 24 48 72 96 120 144 168

C

- Treatment
- Placebo
- AP

CRP (mg/dL)

Time (hrs)

0 24 48 72 96 120 144 168

D

- Treatment

PCT (ng/mL)

Time (hrs)

0 24 48 72 96 120 144 168

- p<0.0001
- p=0.003
- p<0.0001
- p=0.32
Secondary end points
AP treatment reduces ICU length of stay

Mean Length of ICU Stay (ITT, excluding deaths)

![Graph showing mean length of ICU stay for Placebo and AP treatments. The graph indicates that AP treatment reduces ICU length of stay significantly, with a p-value of 0.017.](image-url)
<table>
<thead>
<tr>
<th>Non-renal Clinical Endpoints</th>
<th>Placebo</th>
<th>AP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length ICU stay: days, mean (SD)</td>
<td>25 (18)</td>
<td>11 (8)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Length hospital stay: days, mean (SD)</td>
<td>47 (36)</td>
<td>31 (26)</td>
<td>0.23</td>
</tr>
<tr>
<td>Length of ventilator support: days, median (95% CI)</td>
<td>21 (4;26)</td>
<td>5 (4;29)</td>
<td>0.66</td>
</tr>
<tr>
<td>SOFA Score change 0-7 days: mean (SD)</td>
<td>4 (3)</td>
<td>6 (3)</td>
<td>0.20</td>
</tr>
</tbody>
</table>
# Safety – Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total AEs</strong></td>
<td>130</td>
<td>154</td>
</tr>
<tr>
<td><strong>Serious AEs</strong></td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td><strong>Drug related serious AEs</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Most Common AEs

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

### Most common SAEs

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic Shock</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hypotenstion</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal necrosis</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions

• AP is endogenous protein
  Acts via dephosphorylation of extra-cellular substrates (ATP, LPS), reducing inflammatory response and tissue damage

• Endogenous AP levels are depleted during inflammation / tissue damage

• Well tolerated in clinical trials

• AP replacement significantly improves kidney function in phase IIa trials for Acute Kidney Injury in septic patients
On behalf of the APREN-study group:

Jeroen Schouten  CWZ Nijmegen  The Netherlands  (n=10)
Pierre-François Laterre  UCL Brussels  Belgium  (n=5)
Jean-Louis Vincent  ULB Brussels  Belgium  (n=4)
Bert Beishuizen  VUmc Amsterdam  The Netherlands  (n=2)
Philippe Jorens  University Hospital Antwerp  Belgium  (n=1)
Herbert Spapen  University Hospital Brussels  Belgium  (n=1)

Suzanne Heemskerk
Peter Pickkers  Radboud University Nijmegen MC The Netherlands  (n=13)
Hans van der Hoeven

Trial sponsor

Thank you for your kind attention