A master essay for Medical Pharmaceutical Sciences

Alkaline Phosphatase as a novel drug for Acute Kidney Injury during Septic Shock

A literary survey regarding the evidence of Alkaline Phosphatase as a treatment for Septic Shock, particularly in COVID-19 patients

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Abstract

The mortality of patients in the ICU due to Acute Kidney Injury (AKI) caused by septic shock accounts for more than 50%. Despite this, no real treatment is currently available except for kidney replacement therapy. AKI during sepsis or septic shock may be caused due to gram-negative bacteria which release LPS into the body, activating an anti-inflammatory response. Alkaline Phosphatase (AP) might be the first candidate that would directly lower the toxicity of LPS. Poelstra et al. (1997) were the first research group that researched the natural substrate of AP. They found that the sensitivity to LPS increased when AP was inhibited. Pickkers et al. (2012) researched what effect this would have on the human kidneys. Using Bovine intestinal AP on ICU patients with a gram-negative infection, it was found that the mortality rate decreased. Kiffer-Moreira et al. (2014) developed a human recombinant AP which was more stable while maintaining its specificity. Testing was repeated using this recAP and still showed positive results in the early clinical trials. The phase II clinical trial using recombinant AP did not show significant improvement after seven days. However, after a post hoc analysis, a significant improvement was detected in both treatment effect and all-cause mortality after a 28-day period. A phase III clinical trial is currently running with a COVID-19 cohort recently announced. Looking at the results of earlier studies and the high incidence of AKI among COVID-19 patients, this decision does make sense. However, the underlying mechanism by which this would work, is not researched properly as of this moment, so results are hard to predict.

Introduction

In the ICU, patients with an Acute Kidney Injury (AKI) due to sepsis die twice as often as patients without sepsis (Sakr et al., 2018). For these patients, Renal Replacement Therapy is the most used therapy (Kes & Jukić, 2010). However, this does only aid in the blood filtering for the body. No drug is currently in use that can directly fight the cause of the sepsis, instead of its symptoms.

At this moment, AM-Pharma is in its phase III trial (REVIVAL: REcombinant human alkaline phosphatase SA-AKI surVIVAL trial) with a recombinant alkaline phosphate which targets the LPS released by gram-negative bacteria directly. This would lower the inflammation in the kidneys, preventing and protecting from damage caused by the inflammation. The AM-Pharma Phase III trial is planning to enrol 1400 patients in a randomised, double-blind-placebo-controlled, two-arm, parallel-group, multi-centre trial (AM-Pharma, 2021).

Currently, 90% of COVID-19 patients in the US that received mechanical ventilation also suffered from AKI. When an AKI occurs, it is associated with a poor prognosis (Hirsch et al., 2020). Given the high incidence of COVID-19 in the recent years, a novel drug may offer a solution. Recently, AM-Pharma also started a cohort of COVID-19 patients to test the improvement of all-cause mortality when administrating alkaline phosphate (AM-Pharma, 2021). This will be tested with up to 100 patients. The Netherlands Enterprise Agency has backed research within this cohort with 5 million euros.

This essay will determine how strong the evidence is for a COVID-19 cohort in the phase III REVIVAL trials. To do this, first the background of alkaline phosphatase with LPS as its natural substrate and the effects this interaction has on the body. Then, the research regarding COVID-19 related AKI and whether alkaline phosphatase would be effective as well.

Alkaline Phosphatase and Acute Kidney Injury

Alkaline Phosphatase (AP) is a membrane-bound glycoprotein which aids in the hydrolysis of phosphate monoesters at a high pH optimum (7.4-9.8) (Krishnaswamy & Kenkare, 1970). These enzymes are not only found in higher eukaryotes, but prokaryotes as well (Sharma et al., 2014). APs function as dimeric molecules and contain two Zn^{2+} and one Mg^{2+}. These metal ions are not only essential for enzymatic activity, but are also needed for the conformation of the AP monomer and regulate subunit-subunit interactions indirectly (Hoylaerts et al., 1997).

In humans, four isoenzymes are currently known. These are named after their location within the body. There are the Intestinal AP, Placental AP, Germ cell AP, liver/bone/kidney AP (Sharma et al., 2014). The intestinal AP seems to have several functions: it is involved with pH regulation and bicarbonate secretion, detoxification of bacterial endotoxins and regulation of lipid absorption. Bone AP seems to have a role in bone mineralisation (Peters et al., 2014). For the other isoenzymes, their role is less clear. Still, the serum levels of these isoenzymes are used as markers of disease since their serum level can be used as markers for cancer, bone fractures and cholestasis (Sharma et al., 2014).

Acute kidney injury (AKI) has a high incidence in the ICU: estimations vary between 20% and 50%, contributions to mortality are more than 50% and if a patient does survive, there is a 33% chance of developing chronic kidney disease (Peters et al., 2014). Of all cases of AKI in the ICU, more than 30% is caused by sepsis (Bagshaw et al., 2008). Although its pathogenesis is not yet understood, it is known that the response of the body to an infection leads to an increase of inflammatory mediators, upregulation of nitric oxide synthase (iNOS), and activation of the complement cascade (Peters et al., 2014). During sepsis, the innate immune system recognises pathogens or pathogen-associated

molecular patterns (PAMPs) through pathogen recognitions receptors (PRRs) such as Toll-like receptors (TLRs). This allows the innate immune system to trigger an inflammatory response.

One of these pathogen associated molecular patterns is the polysaccharide (LPS) originating from the outer membrane of gram-negative bacteria (Peters et al., 2014). In the body, LPS binds with LPS-binding protein to TLR4, which in turn activates NF-κB. This starts a cascade, which results in haematopoiesis, phagocytosis and recruitment of leukocytes in the affected area (Cavaillon et al., 2003). When this occurs in the kidney, oxidative stress increases in the lower segments of the proximal tubules inflammatory cells are activated. This, paired with complement and coagulation pathways activation, upregulation of TLR4 and nitrogen species, and protease activation, results in functional changes in epithelial and endothelial cells within the kidney (Bajwa et al., 2009). These changes may lead to tubular apoptosis. Although its high incidence is troublesome, no treatments are available that can directly stop this process from occurring.

AP function in the body

Although AP has been researched since 1943, its natural substrates were not found until 1997 (Poelstra et al., 1997). The research group of Poelstra found that AP is able to dephosphorylate the toxic moiety of LPS (lipid A), turning diphosphoryl lipid A into the less toxic monophosphoryl lipid A (Poelstra et al., 1997). This prevents LPS from starting the inflammation cascade in the body. This was done by testing whether intestinal AP could dephosphorylate LPS originating from *Escherichia coli* and *Salmonella minnesota* at a pH of 5, 7.5, and 9.

First, male Wistar rat intestinal cryostat sections were stained for phosphatase activity using the method of Wachstein and Meisel (Poelstra et al., 1997). LSP of E.coli and S. minnesota R595 both yielded a stain along the epithelial layer of the intestinal crypts of all rats that were examined. When using β-glycerophosphate as a substrate instead, an identical pattern was found, although the intensity was much higher. When adding L-Phenylalanine, the stains were much less intense when using either LPS or β-glycerophosphate. This is summed up in figure 1.

	LPS from:			
	E. coli	*S. minnesota*	β-gP	None
pH 5.0	–	–	+++	–
pH 7.5	++	+	+++	–
pH 9.0	–	–	+++	–
pH 7.5 with L-phenylalanine	±	ND	+	–

β-gP, β-glycerophosphate; –, none; +, moderate; ++, medium; +++, strong staining; ND, not done.

Figure 1: Results of staining the male Wistar rat intestinal cryostat sections. (taken from Poelstra et al., 1997)

Then, the research group tested the sensitivity for LPS in male Wistar rats after administering levamisole, an AP inhibitor (Poelstra et al., 1997). If no infection was initiated by the research group, the rats showed neither any abnormal behaviour nor significant change in body weight or temperature compared to the control group. After being infected with *E. coli* bacteria and given levamisole, a significant difference was noted, however. The addition of levamisole to the infection raised the mortality of the rats from 35% to 90% in a 24h time period. Their body temperature was also significantly lower. Trying the same experiment using S. aureus (a gram-positive bacterium) did not give this significant change. This is summed up in figure 2.

These results indicate that the interaction between AP and LPS originating from gram-negative bacteria is beneficial to the survival of these rats.

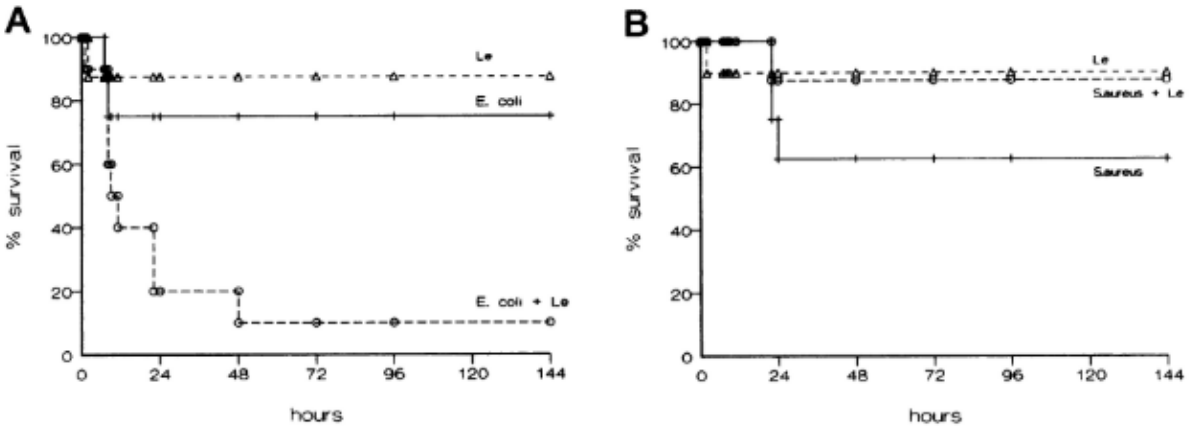

Figure 2: Survival time of rats after receiving levamisole and/or either a gram-negative or gram-positive bacterium. (Edited from Poelstra et al., 1997)

Koyama et al. (2002) found similar results. They administered LPS orally to Wistar male rats. Afterwards the Duodenum was extracted to examine AP activity. They found that AP activity in the crude extracts of the duodenum after oral LPS administration was elevated up to four hours. After this raise, the level decreased for six to eight hours and recovered after 24 hours (Koyama et al., 2002).

Looking at serum levels of LPS in the next experiment, the concentration of LPS increased after two hours and decreased after six hours after administration. However, with addition of L-Phe (an intestinal AP inhibitor), concentrations increased significantly after one hour. Pre-treating the LPS with AP decreased toxicity. However, when LPS was pre-treated with both AP and L-Phe, this reduction was restrained. This is consistent with the earlier results.

Then, AP was tested in human aortic endothelial cells (HAECs) (Koyama et al., 2002). After pre-treating LPS for three hours with or without intestinal AP, the HAECs were incubating with the resulting LPS, after which cell viability was measured. The researchers found that the cell viability was higher when the LPS which was pre-treated with AP was added as opposed to the LPS which did not get pre-treated. However, this was only observed at the optimal pH of AP or at a pH of 8.0. At a pH of 7.4, the effects was much smaller, and can mainly be seen when low levels of LPS were used. When incubating with AP alone, no difference was observed. These results show that AP not only interacts among rat intestinal cells, but among human cells as well.

AP improves Kidney function

The research group of Pickkers has been the main research group that has studied the effects of AP on kidney failure due to LPS originating from septic shock. Septic shock has a high variability in its clinical manifestations, which typically makes it difficult to define a patient group (Khilnani, 2012). Because of this, a small, well-defined group (namely patients with acute onset of end-organ dysfunction, including sustained hypotension, present for twelve hours or less) was chosen to illustrate results more clearly. In later studies, this group was even more precisely defined, by only allowing patients with severe sepsis or septic shock and AKI (Pickkers et al., 2012). It can be argued that this specific choice of patient group is the reason why the first trials were more effective than predecessors.

In 2009, the results from a phase IIa trial were released in which bovine AP was administered to ICU patients presenting with a proven or suspected gram-negative bacterial infection (Heemskerk et al., 2009). Clinical parameters were determined before, during and after administration. Sepsis-Related

Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation were recorded for all patients.

Observations showed no drug-related serious adverse effects. After treatment, median plasma creatine levels declined from 91 to 70 µmol/L. Also, the 28-day overall mortality was 24% for the AP-treated group compared to 36% for the placebo-treated group. And the mortality rate of patients with an AKI tended to be lower than the placebo-treated group as well (27% vs 60%). However, this trial also had enrolled patients without AKI. Because of this, the results were not completely representative for patients who this drug was intended for (Heemskerk et al., 2009).

In 2012, a similar trial was conducted (Pickkers et al., 2012). In this trial, renal function was measured combined with a panel of urinary biomarkers of renal injury instead. Here, 36 adult patients with severe sepsis or septic shock and AKI were given a bolus injection of bolus AP or a placebo. Arterial blood and urine were continually collected during the 48 hours of treatment. After that, they were collected once daily until seven days had passed. These samples were used to determine the levels of Urinary KIM-1, NGAL, IL-8, GSTA1-1, GSTP1-1, LBP, and IL-6. Routine haematology, biochemistry and CRP were also evaluated.

Results showed an improvement of several renal variables in the AP group compared to the placebo group. A selection of improved renal markers can be seen in figure 3. These results indicate that renal function improves when AP was administered after an AKI is established in a patient (Pickkers et al., 2012).

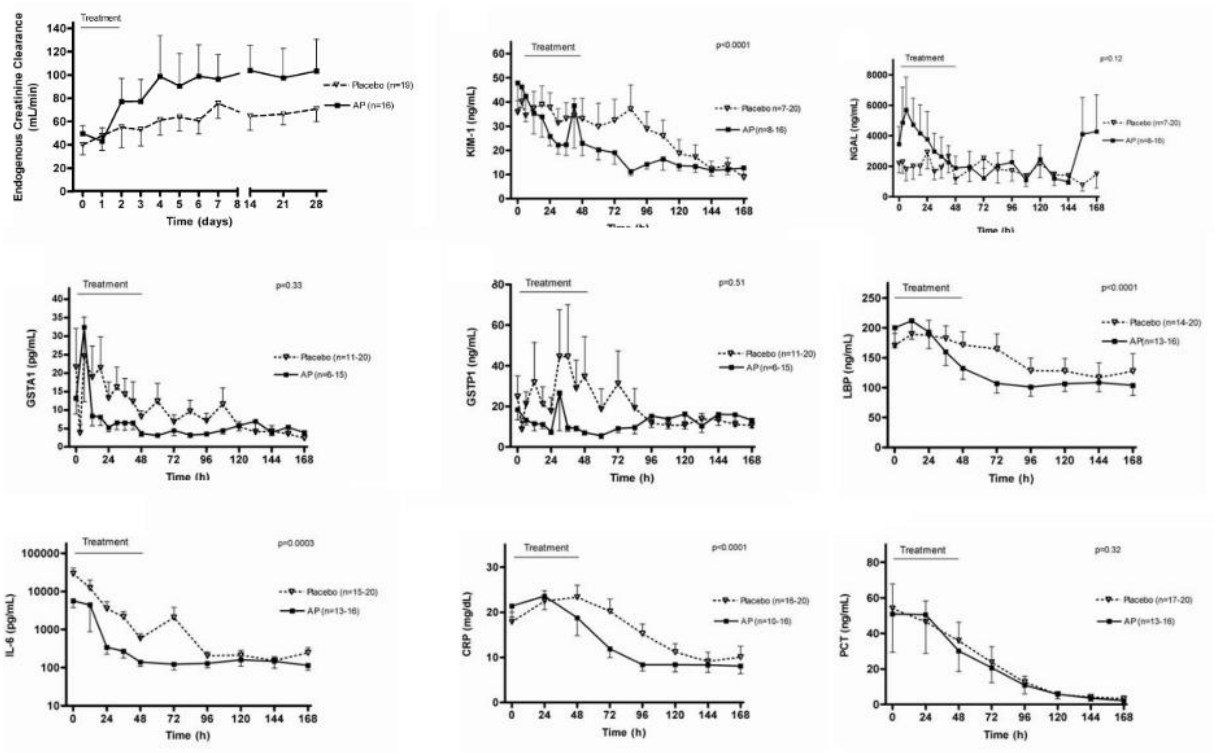

Figure 3: Renal markers in patients with an AKI after administration of either AP or a placebo. (Edited from Pickkers et al., 2012)

Recombinant AP

Up to this point, bovine intestinal AP was used for trials. In 2014, the research group of Kiffer-Moreira developed a heat-stable, chimeric human AP whose therapeutic potential was higher than that of the bovine intestinal AP (Kiffer-Moreira et al., 2014). Earlier, another recombinant AP was created by this research group, which was able to replace AP in Akp2^{-}/$^{-}$ Mice, preventing hypophosphatasia (Yadav et al., 2011).

After recombination of AP had been proven to be possible, a new type of combination was developed. By subsidising the flexible crown domain of human intestinal AP with human placental AP, an AP was formed with the structural folding of intestinal AP. This recombinant AP (recAP, also referenced as chimeric AP (chimAP)) had greater stability, active site Zn^{2+} binding, greater transphosphorylation, narrower specificity, and still have a comparable selectivity for LPS (Kiffer-Moreira et al., 2014).

To test this recAP's properties, first the rate of catalytic Zn ion dissociation at physiological pH was determined. These rates can be seen in Figure 4.

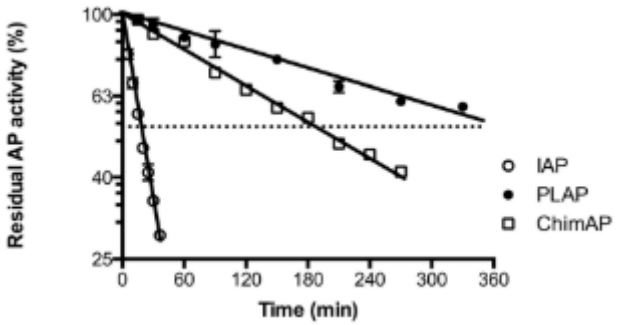

Figure 4: Rate of AP disappearance upon dissociation of Zn^{2+} of intestinal AP, human placental AP and chimeric AP at a pH of 7.4. (taken from Kiffer-Moreira et al., 2014)

Then, overall enzyme efficiency was tested using several different substrates, including LPS. Efficiency was measured as the rate of phosphate formation versus substrate concentration. These results are shown in figure 5.

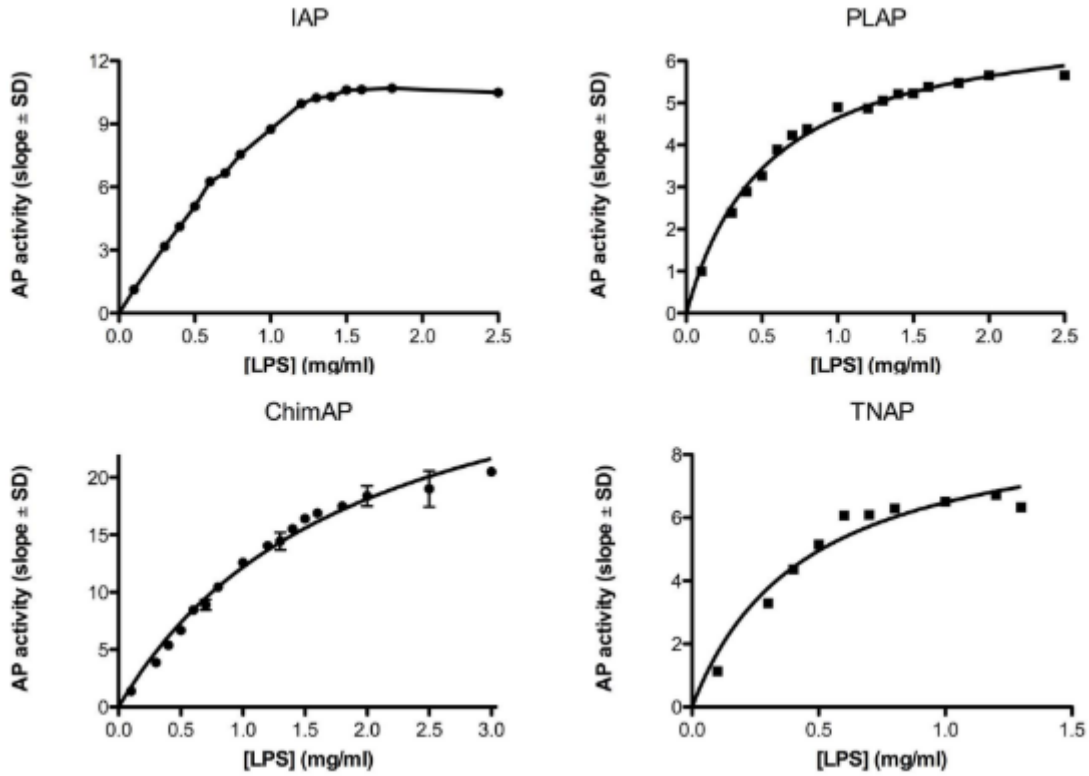

Figure 5: Efficiency of intestinal AP, human placental AP, chimeric AP and tissue nonspecific AP. (taken from Kiffer-Moreira et al., 2014)

After that, the enzyme stability was compared between these several types of AP. This was done via unfolding in guanidinium hydrochloride and via heat activation studies. Heat activation was either tested at different temperatures for 10 minutes, or at different time intervals at 65 ˚C. The results for these experiments can be seen in figure 6.

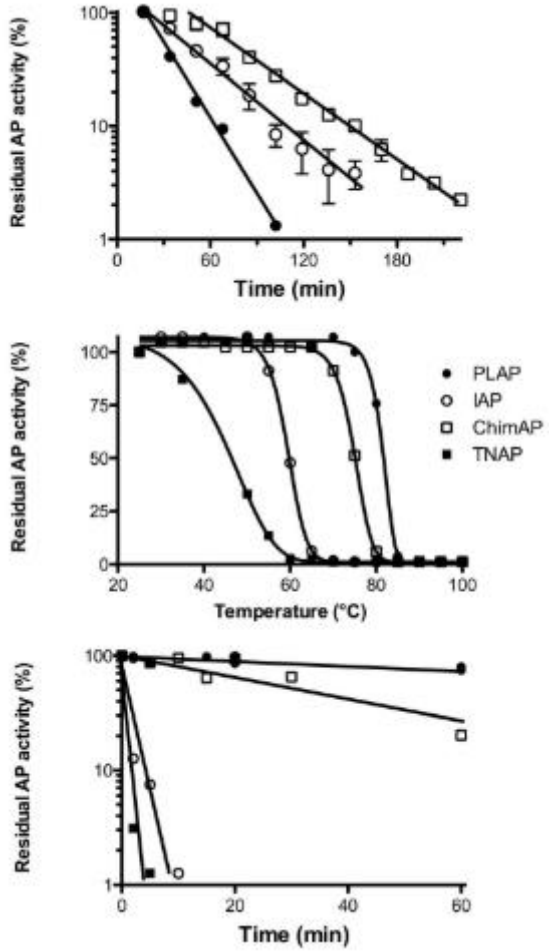

Figure 6: Plot of residual enzyme activity after denaturing, heat inactivation after 10 minutes, or heat activation at 65 ˚C. (taken from Kiffer-Moreira et al., 2014)

These results show that this recombinant AP is more stabile than intestinal AP, while still being sufficiently selective for LPS. This makes this human AP a better drug candidate than the previously bovine intestinal AP.

Recombinant AP tested in mice

Using the recombinant AP, a new set of trials was set up to test the improvement of renal function in patients with sepsis-associated acute kidney injury when using this enzyme.

This was first done as an animal study (Peters et al., 2015). Sprague-Dawly rats were given either a placebo, LPS or LPS and recAP after a baseline renal function was established. Plasma samples were taken from the rats both seven days before the experiment and 1.5 hours after administration of LPS or placebo. After two hours of initial administration, either placebo or recAP was administered. Afterwards, urine was collected, and the animals were killed for processing of the kidneys after 24 hours.

The research group found that after 1.5 hours, LPS treatment increased plasma cytokine levels and abnormalities in plasma parameters. The rats themselves also displays piloerection, diarrhoea and reduced spontaneous acivity. They also showed that this was paired with decreased renal function through FITC-sinistrin half life. Comparing the cytokine markers between rats that received recAP or placebo showed a reduction in these markers which indicates a reduction in renal damage due to LPS.

The researchers also incubated ciPTEC human renal cell line with LPS, producing an AKI-like effect. They observed a higher extracellular ATP concentration after LPS incubation with the cell line. This was not observed if recAP had been given beforehand. Instead, the level of adenoside was higher, indicating that the ATP had been converted into AMP and adenosine. This can be seen in figure 7. These results show that recAP also is capable in protecting the kidney after an AKI (Peters et al., 2015).

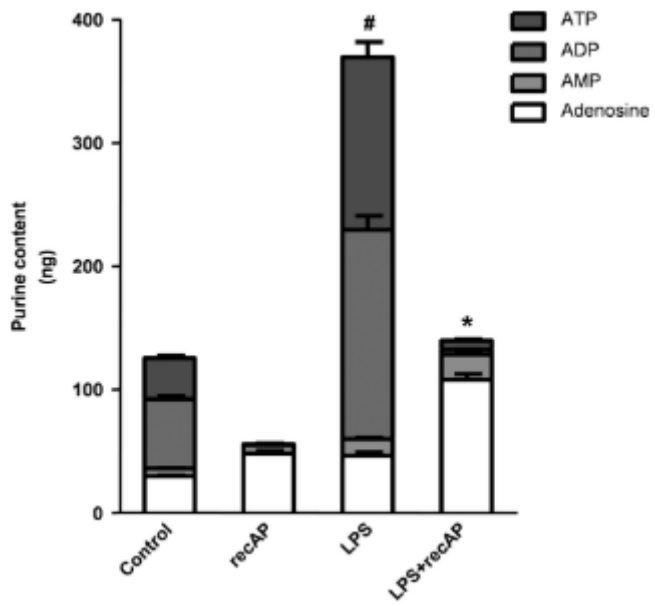

Figure 7: The effects of recAP on ATP and ADP release in LPS-induced ciPTEC cells. (taken from Peters et al., 2015)

A renal protective mechanism of recAP was proposed as well by the research group (Peters et al., 2015). LPS binds to TLR4, which is expressed on the proximal tubute epithelial cells. This normally provokes an inflammatory response resulting in the release of pro-inflammatory cytokines and ADP and ATP. Both ADP and ATP signal through purine P2 receptors, which further enhances the pro-inflammatory cascade. RecAP dephosphorylates LPS, detoxyfying it in the process, resulting in a molecule that still binds to TLR4. However, it is incapable of activating the initial inflammatory

cascade. In addition, recAP dephosphorylates both ADP and ATP into adenosine, which binds adenosine receptors. This results in a tissue-protective and anti-inflammatory effect. This double protective mechanism seems to be the reason why AP is capable of its anti-inflammatory effect specifically in the kidneys (Peters et al., 2015).

First-in-human study

After animal studies were deemed successful, human studies were performed as well (Peters et al., 2016). The first-in-human study to determine the pharmacokinetics, safety and tolerability of recAP were performed in 2016. The results were used to develop a population pharmacokinetic model for dose selection which was used in further patient studies. The first part of the study called for a single dose escalation model with each patient receiving a single dose of recAP (200, 500, 1000 or 2000 U/kg) or placebo. The second part of the study called for three doses of recAP (500 or 1000 U/kg) or placebo by administering a 1h intravenous injection on consecutive days. Blood samples were taken before administration and regularly after administration. This was used to determine serum recAP concentrations used to determine pharmacokinetic properties of recAP and create a population pharmacokinetic model for future research.

The research group found that both the single and multiple infusions were well tolerated and did not lead to safety concerns (Peters et al., 2016). No severe adverse events were noted, with the most common events being headaches, postural dizziness, and local swelling. The recAP serum concentrations reached a peak right at the end of infusion and ranged in the single dose cohort between 1715 to 26,253 ng/ml (Peters et al., 2016). After infusion ended, serum concentrations would decrease in a multiphasic manner, showing less than 5% remained after 24 hours after the infusion was initiated. Still, recAP was detectable in the body after 120 hours in all single dose groups and after 192 hours if the dose was 500 U/kg or higher. AP activity followed a similar pattern. With the multiple dosing group, recAP was detectable at least up to 240 hours after the last dose. For the pharmacokinetics, a four-compartment model seemed to resemble the data when using a proportional error structure most closely (Peters et al., 2016).

Phase II trial

Using the collected information, a phase II study was initiated in 2018 (Pickkers et al., 2018). 301 patients were divided into 4 cohorts: they would receive either 0.4 mg/kg, 0.8 mg/kg, or 1.6 mg/kg recAP or placebo once daily for three days. Creatine clearance was measured for seven days to calculate a mean daily creatine clearance. Afterwards, the optimal dosage was selected based on tolerability (1.6 mg/kg) and compared to placebo by comparing blood urea nitrogen clearance up through day 28.

RecAP did not seem to significantly improve short-term kidney function compared to the placebo cohort in the first seven days of the study, which was the primary endpoint (Pickkers et al., 2018). The research group found several possible explanations for this result. Analysis found that, despite randomisation, an imbalance in kidney function between the four cohorts was present, with the more severe kidney dysfunction being present in the recAP groups. This can account for a less than expected outcome in the first week. Also, the seven-day time frame which was used might not have been optimal. A post hoc analysis of the data after the first seven days showed a significant increase of kidney function and decrease of all-cause mortality after 28 days (Pickkers et al., 2018). This indicates that, although recAP does not increase chances of septic patients on the short term, it can be effective when used for a prolonged time.

Expectations for the future

Although the phase II trial has not ended as successfully as expected, a phase III trial was announced in 2019, which has yet to publish its results. In 2021, it was also announced that this phase III trial would contain a COVID-19 cohort, which would be up to 100 patients from the 1600 total patients (AM-Pharma, 2021). This study focuses on the effects of recAP on 28-day mortality among patients admitted to the ICU with AKI induced by sepsis.

Since COVID-19 patients are among the largest patient pool currently during the pandemic, this is not completely an unfounded decision. As this novel disease is being studied, it has revealed that AKI's are common in COVID-19 patients (Nadim et al., 2020). Also, not much is known about the exact pathogenesis or optimal treatment of COVID-19-associated AKI. A treatment is necessary however, since the mortality of COVID-19 patients with renal impairment is 50% (Gasparini et al., 2021). The question remains however how much of an impact APs will make.

With the results which have been achieved so far, a positive result can be expected. Since this study seems to take a longer time period to see results, a result more in line of the phase II clinical trial can be expected. However, since the cohort will consist of COVID-19 patients, the underlying pathogenesis with these patients might differ. Seeing that the SARS-CoV-2 virus is not a gram-negative bacterium, it will depend on whether the virus directly causes the AKI, or whether the virus allows gram-negative bacteria to enter the body more easily.

The Conference Chairs of the 25th ADQI consensus committee has recently compiled a consensus report regarding this matter (Nadim et al., 2020). They describe that the pathogenesis of AKI in patients with COVID-19 is likely multifunctional, with possibilities of both direct damage to the kidney due to the virus and indirect mechanisms as a result of systemic effects or other organs. This, however, does explain how AP would be able to interact with the SARS-CoV-2 virus.

A possible mechanism of action could explain why AP was chosen as a therapy for COVID-19 patients. In most cases, a SARS-CoV-2 infection may be asymptomatic or cause mild symptoms. However, in 10-20% of cases an infection progresses to interstitial pneumonia and acute respiratory distress syndrome (Soy et al., 2020). In these cases, the serum level of ferritin and the D-dimer levels are disproportionate to the severity of infection. This is paired with a low number of natural killer cells and cytotoxic T-cells, and a tendency for disseminated intravascular coagulation. Monocytes and macrophages were increased, on the other hand. These innate immune cells caused an increased level of pro-inflammatory cytokines, such as IL-6, IL-1, TNF- α, and IFN-γ. In severe cases, this release may create a systemic cytokine storm (Tang et al., 2020). During a cytokine storm, acute systemic inflammation symptoms and secondary organ dysfunction may occur (Mehta & Fajgenbaum, 2021). This can lead to a sudden drop of blood pressure, organ failure, and ultimately death.

Although a cytokine storm in itself can be fatal already, one of its consequences is an increased vascular permeability (Soy et al., 2020). When this changes the permeability of the intestines, bacterial translocation may occur, increasing the LPS levels in the blood (Cardinale et al., 2020). This in turn may increase the inflammation in the body, creating a vicious cycle. Here, AP may play a positive role. However, since this is only a part of the mechanism behind a cytokine storm, AP may be an insufficient therapy.

A proposed interaction between the SARS-CoV-2 virus and LPS might give another mechanism of action. Petruk et al. has done research regarding this matter (Petruk et al., 2020). Their research found that there is a link between high LPS levels in the blood, metabolic syndrome, and the severity of COVID-19. Using THP1-XBlue-CD14 cells, they studies the proinflammatory effects of the S Protein of the SARS-CoV-2 virus with of without LPS present. It was shown that NF-κB activation was boosted when low levels of LPS were added. This response was not present when the LPS was added without the S spike. Then, in an experimental mouse model, 2 µg LPS was injected subcutaneously with or without S protein (Petruk et al., 2020). Earlier research had already shown that 25 µg LPS is typically needed for a significant response. However, the presence of the S protein significantly increased NF-κB activation in the mice. This response was not observed when the S protein was administered without the LPS. They proposed a mechanism where LPS aggregates can bind to S proteins, disaggregating the LPS in the process (Petruk et al., 2020). After dissociation, the free LPS then can bind more effectively to the TLR4/MD2 complex, activation downstream signalling. At high S protein concentrations, it is also possible that S protein-LPS complexes form large aggregates, which may also promote inflammatory responses.

Based on these results, a proposed mechanism may be that the dephosphorylation of LPS already present in the body inhibits the interaction between LPS and SARS-CoV-2, and rendering it unable to bind to TLR4, preventing the downstream cascade. This might decrease the severity of the sepsis. This appears to not have been researched yet, however.

Conclusion

This essay has set out to weigh the evidence currently available to justify a COVID-19 cohort in the ongoing REVIVAL phase III clinical trial.

The prove of concept of AP use for renal improvement in septic patients has clearly been established. Several phase II clinical trials using bovine intestinal AP have shown that creatine levels and all-rate mortality improved. AP also improved renal markers, indicating improvement of kidney function after administration. Using the recAP, an animal study showed the double protective function that could be provided to the kidneys. The first-in-human study showed that recAP was well tolerated.

The preceding phase II study was not successful in achieving its primary endpoint, however. This can be explained when considering the primary endpoint called for a lowering of all-rate mortality in seven days. With a ad hoc analysis, a significant improvement was found after 28 days. This point was taken into consideration for the ongoing phase III trial. Taking all these results together, it would make sense that future trials have a positive outcome as well and, in this regard, the evidence for overall successful results for the phase III clinical trial is present.

The evidence for the COVID-19 cohort is less strong. The main idea behind an AP therapy during COVID-19 seems to be related to the cytokine storm which occurs in severely ill patients, which may raise the level of LPS in the body and creates a vicious cycle. If AP can prevent this from happening of reduce the severity by breaking the cycle, this would be a positive. Whether AP is capable of doing so in not yet known, however. Also, some research has shown an interaction between the SARS-CoV-2 virus and LPS present in the body. This may be a pathway in which AP might show another benefit to patients. The evidence to prove such a pathway is lacking, however. As long as the link between the SARS-CoV-2 virus and LPS is not researched properly, the outcome of the phase III trial will be hard to predict and could go either way.

Still, with the high incidence of AKI in patients in the ICU, particularly in COVID-19 patients, a novel treatment is necessary. With the high mortality rate and no other options currently, it is understandable why the Netherlands Enterprise Agency has backed this trial, even if it is a long shot. Once research has been published showing an improvement off all-rate mortality in COVID-19 patients, the evidence will be strong enough, making way for follow-up research with a larger cohort of COVID-19 patients. In conclusion, this will al depend on the results of the ongoing phase III trial.

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