Rationale for apheresis of CRP from the blood plasma of COVID-19 patients with beginning or acute organ damage

Summary
The rationale for extracorporeal removal of C-reactive protein (CRP) in patients with SARS-CoV-2 infection is to limit or prevent activation of the complement system by lowering the CRP concentration in the blood. As a result, a general stabilization of the clinical and circulatory system should occur. In addition, a later limitation of performance due to fibrosis of the lungs could be reduced.

CRP apheresis with the adsorber PentraSorb®CRP can be performed as a complementary therapeutic measure in patients suffering from COVID-19 (22).

Previous clinical studies on CRP apheresis have demonstrated a safe, efficient and selective lowering of plasma levels of C-reactive protein. The clinical data to date provide clear evidence that CRP depletion can reduce systemic inflammation and tissue damage.

PentraSorb®CRP is a medical device (18). It bears the CE mark and can be used for the removal of CRP from human plasma. CRP apheresis can be reimbursed in Germany via additional fees.

COVID-19 and immunopathology

The pandemic infection with SARS-CoV-2 has affected or caused the death of numerous people worldwide within a short time. The number of cases continues to rise worldwide, although there are regional differences. In Germany, too, about 3% of the currently detected infected persons are under intensive medical treatment, of which again about 80% require respiration (2). The mortality rate ranges from 1.8% in Germany to 13% in France; in the age group over 60 years it is more than 20% (9, 11). The current therapeutic approach focuses on the symptomatic treatment of acute respiratory distress syndrome (ARDS). This is the main cause of mortality, followed by cardiological and septic complications.

Clinical observations worldwide show that some immunocompetent patients with severe COVID-19 symptoms - as in SARS - experience systemic excessive inflammation, colloquially called cytokine storm (21, 31-33). This overreaction of the immune system is an often underestimated and difficult to control complication. It often leads to a fulminant, fatal hypercytokinaemia or to terminal organ failure.

The course of SARS and COVID-19 shows a strong pro-inflammatory component with time peaks. The first increase in cytokines reflects the primary response to the virus. Subsequently, a large proportion of patients heal spontaneously and become immune to COVID-19, while a smaller proportion of patients (3%) - but a proportion of about 20% among those aged >60 years - develop moderate to severe symptoms. This is presumably also caused by global hypoxemia, which leads to early tissue damage not only in the lungs but also in the tissues that consume more oxygen (heart, liver, kidneys, possibly brain) (10). Post mortem, therefore, histopathological signs of tissue loss and fibrotic remodelling processes are not only diagnosed in the lungs (5).

Serologically, IL-6 and CRP impress with strong increases each. IL-6 is often used as a prognostic marker of inflammation (26). The CRP concentration often correlates with the overall clinical picture and is strongly elevated (>200 mg/L) even over several days, especially in severely ill patients.

CRP plays a dominant role in these pathophysiological processes. CRP is a central molecule of the innate immune system ("innate immunity") and part of a complex immune cascade that can lead to tissue destruction. Highly elevated CRP concentrations are often associated with hyperinflammation or organ dysfunction.
In ARDS, elevated CRP concentrations in alveolar exudate have also been described and CRP inhibition of the surfactant (34).

In the acute clinical course of a CORVID-19 infection, immunosuppressive therapy therefore appears to be an obvious choice (1, 19, 29, 30-32). Currently used therapeutic measures include immunoglobulins (IVIG), cytokine blockades (IL-1, IL-6, TNF), inhibition of janus kinase (JAK). Unfortunately, none of these potential therapeutics is currently approved for the treatment of COVID-19, their clinical benefit has not yet been proven and finally they will only gradually become widely available.

Steroids are apparently limited in their therapeutic efficiency and showed contradictory effects on the course of the disease during the SARS epidemic in 2002/03 (3, 27). With regard to the desired rapid reduction of CRP to prevent organ damage, all these drug-based therapeutic approaches are not effective enough.

Against this background, the rapid reduction of CRP levels in medium and severe courses of COVID-19 and imminent or incipient organ failure is therefore a potential therapeutic approach (14, 22).

With the PentraSorb®CRP, a regenerable, CE-marked and clinically tested specific adsorber is available that effectively lowers the CRP concentration in the blood. This should have a positive effect on the course of the disease with COVID-19, because CRP apheresis effectively lowers the blood levels of CRP within a few hours.

C-reactive protein (CRP)

CRP is an evolutionary highly conserved acute phase protein, whose concentration in the blood increases in infectious and inflammatory diseases within a few hours after a stimulus. Therefore, it has been established as a sensitive, reliable and early indicator/biomarker for infections and tissue-destroying processes (14). In addition, CRP triggers tissue damage and is thus also causally involved in its extent.

Clinical studies in various disciplines have shown that an increased CRP concentration correlates with more tissue damage, more inflammation, more severe symptoms, longer hospitalisation and a poorer long-term prognosis.

The pathophysiologically relevant molecular mechanisms of CRP are largely known. CRP irreversibly binds to the outer membrane of damaged but not healthy cells. The binding of CRP leads to the activation of complement with subsequent binding of monocytes, thus

triggering the mechanisms of the innate immune system. As a consequence, the inflammation and not only SARS CoV-2 leads to fibrotic and scarring remodelling processes in the affected tissue. The influence of CRP on myocardial infarction is particularly well studied. The results can be generalized to other CRP-mediated, tissue-destroying processes.

Infection with coronavirus

The clinical picture of severe acute respiratory syndrome (SARS) corresponds to atypical pneumonia. The causative agent of SARS is now known as the SARS-associated coronavirus (SARS-CoV), which caused an epidemic in Southeast Asia in 2002/2003 with about one thousand deaths (4, 7, 8, 13, 15-17).

At that time, increased concentrations of proinflammatory cytokines and their negative prognostic influence were observed early after infection (23, 24). The cellular processes of infection and primary activation of the innate immune system have been sufficiently elucidated in the coronavirus SARS-CoV and MERS-CoV (6, 20). Therefore, similar inflammatory and pathophysiological mechanisms can be assumed for SARS-CoV-2.

The interaction of viral infection and immune response is obviously the pathophysiological interface. This leads to an activation of immunocompetent cells and the release of a multitude of primary and secondary inflammation mediators.

According to previous findings, respiratory distress or systemic oxygen deficiency often developed rapidly in the course of the infection, with about 20% of the affected persons requiring intensive treatment including oxygen supply. Some of these patients also developed kidney failure or sepsis (12).

The hospital stay of the severe courses of the disease was up to 30 days. A restitutio ad integrum was not achieved. Even with milder courses, pulmonary fibrosis was still diagnosed later in the follow-up.

According to recent publications from Wuhan, SARS-CoV-2 causes acute and chronic damage to the cardiovascular system in addition to respiratory symptoms. The high incidence of cardiovascular symptoms and therapy failure in advanced disease may explain the high mortality of patients with cardiovascular disease, especially elderly patients.

Clinical and immunological findings from Italy, which were collected in younger SARS patients, also indicate additional systemic immunological and inflammatory disorders. Excessive immune responses-as a reaction to SARS-CoV-2 infection-can lead to tissue damage and thus to massive impairment of organ function (5,25, 28). The pronounced disorders of the cardiovascular system, which also affect organ perfusion and microcirculation, favour the development of a dysfunctional syndrome of various organs. This is the most frequent cause of death in this younger group of patients, i.e. multi-organ failure becomes part of this infectious disease.

Previous experience with CRP apheresis

Extracorporeal CRP elimination is a therapeutic apheresis procedure. The term therapeutic apheresis refers to general medical procedures whose therapeutic effect is based on the elimination of defined components of the blood to which a pathogenic function is ascribed in the context of disease processes.

To remove the pathogenic substances, the plasma is separated from the bloodstream and passed over an adsorber in which certain molecules - in this case CRP - are retained. The purified plasma is then reunited with the solid blood components and returned to the patient.

Most experience in CRP apheresis has been gained in the treatment of myocardial infarction. In the so-called CAMI-1 study, in addition to the safety of the procedure, the efficient reduction of the CRP level by the adsorber PentraSorb® CRP, the direct correlation between CRP progression and cardiological outcome was shown for the first time. It could be demonstrated that the resulting infarct size is directly proportional to the CRP load in the first days after infarction. Conversely, the pumping function of the heart (LVEF) is indirectly proportional to the CRP load. An artificial reduction of the CRP level during this time resulted in smaller infarcts and a better LVEF. No undesirable effects of CRP apheresis were observed.

The ubiquitous molecular pathomechanism of CRP suggests that the tissue protective effect of CRP apheresis also occurs in tissues other than the lung. Singular healing experiments in acute pancreatitis and sepsis (treated in Braunschweig, Essen and Flensburg) showed that depletion of CRP also has a positive effect on clinical, circulatory and organ functions. The safety of the therapy procedure also for these acute and problematic clinical pictures could also be proven (Dr. Ries, pers. communication).

CRP apheresis with COVID-19

CRP apheresis is an anti-inflammatory, antinecrotic therapy that works quickly and effectively. Within hours, the CRP concentration is reduced to a degree that is currently not achievable with medication. The indication for apheresis is based on laboratory findings of IL-6 and CRP as well as the clinical symptoms. The curves of the blood parameters and their correlation with the clinical courses result in the therapeutic indication for patients with moderate courses and few comorbidities. Here, early intervention could pathophysiologically prevent slipping into more severe courses and organ damage.
Patients with severe courses could be intercepted analogous to the experiences made with patients with acute pancreatitis and SIRS, so that a response to catecholamine administration is guaranteed and renal complications are prevented.

In principle, apheresis should be performed until a stable and sustained reduction of the CRP concentration in the patient's blood below 75mg/L is achieved. A daily treatment over 3-7 days should be considered. The treatment time is about 5 hours daily, and the treated plasma volume is then about 6000ml. Access to the extracorporeal circulation can be peripheral or central. The treatment does not necessarily have to be carried out in an intensive care unit, true to the motto "the sooner the better".

Accordingly, the following criteria should be suitable for a good treatment approach in patients with moderately severe symptoms:

- PCR test positive for SARS CoV-2
- Conspicuous large blood count on admission
- When a conspicuous chest x-ray is taken
- CRP ≥ 25 mg/l and/or
- Interleukin 6 ≥ 25 pg/ml
- BISAP ≥ 2 and/or
- qSOFA score ≤ 2 and/or
- Apache II Score ≤ 8
- Legal capacity

Target parameters/criteria for the effectiveness of apheresis treatment would therefore be

- Tissue damage of the lung and heart, determined by imaging techniques
- Pulmonary and cardiac events
- CRP kinetics, permanent reduction of the CRP concentration to <100 mg/L
- Inflammatory biomarkers: IL-1, IL-6, neopterin, PCT
- Improvement of the clinical picture
- cardiovascular, respiratory and renal SOFA score
- Pulmonary function
- Cardiac function
- Renal function
- Horovitz score
- Response to vasopressor therapy
- Duration of the obligation to ventilate

Literature

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