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

Summary

The rationale for using C-reactive protein apheresis (CRP) in patients with COVID-19 is to limit or prevent activation of the complement system by lowering the CRP concentration in the blood. Immediately afterwards, a general stabilization of the clinical and circulatory system should follow, as well as a reduction of pulmonary fibrosis.

CRP apheresis with the adsorber PentraSorb® CRP could be performed as an additional therapeutic measure in patients with a COVID-19 infection and life-threatening organ damage (22).

Clinical studies on CRP apheresis to date have demonstrated a safe, efficient and selective lowering of plasma levels. 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

By mid-March 2020, pandemic coronavirus infection 2019 (COVID-19) had been confirmed in over 180,000 people worldwide (2). The number of cases is currently rising dramatically outside China, but with regional variations. The mortality rate is about 1-4%; in the age group over 60 years it is more than 20% (9, 11). The current therapeutic approach focuses on the 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 - have systemic hyperinflammation, 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 disease course of SARS and thus also of COVID-19 infection shows a strong proinflammatory component with temporal peaks. The first increase in cytokines reflects the primary reaction to the infection. Subsequently, a large proportion of patients develop self-healing and immunity to COVID-19, while a smaller proportion of patients, but a proportion of about 20% among those aged >60 years, develop moderate to severe symptoms. This is probably due to lack of oxygen saturation and respiratory acidosis in the tissues, which are accompanied by inflammatory crises (10). Post mortem, histopathological signs of tissue death and fibrotic remodelling processes are diagnosed in the lung (5).

Serologically, IL-6 and CRP impress with strong increases each. IL6 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 is dominantly involved in these pathophysiological processes. CRP is a central molecule of the innate immune system ("innate immunity"). The acute phase protein is part of a complex immune cascade that can lead to tissue destruction. Highly elevated CRP concentrations are thus often associated with hyperinflammation or organ dysfunction.

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, some of these potential therapeutics are not widely available and their clinical benefit is not yet proven.

Steroids are apparently limited in their therapeutic efficacy and showed contradictory effects on disease progression in the SARS epidemic of 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 the CRP level in medium and severe courses of COVID-19 and threatening or incipient organ failure is therefore a potential therapeutic approach (14, 22).

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

C-reactive protein (CRP)

The 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 in particular and is thus causally involved in its enlargement.

Clinical studies in various disciplines have shown that an increased CRP concentration correlates with more tissue damage, more inflammation, more severe symptoms, longer hospitalization 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 then leads to the activation of complement with subsequent binding of monocytes, thus triggering the mechanisms of the innate immune system. As a consequence, these inflammatory processes lead 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 generalised and transferred to other CRP-mediated, tissue-destroying processes.

Infection with coronaviruses

The clinical picture of severe acute respiratory syndrome (SARS) is that of atypical pneumonia. The causative agent of SARS is now known as 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).

Early after infection, increased concentrations of proinflammatory cytokines and their negative prognostic influence were observed (23, 24). The cellular processes of infection and primary activation of the innate immune system have been sufficiently elucidated in the coronaviruses SARS-CoV and MERS-CoV (6, 20). Therefore, similar inflammatory and pathophysiological mechanisms can be assumed for SARS-CoV2.

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 increased rapidly during the course of the infection, with about 20% of those affected requiring intensive treatment including oxygenation. Some of these patients also developed kidney failure or sepsis (12).

The severe courses of the disease lasted 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 not only respiratory symptoms but also acute and chronic damage to the cardiovascular system. 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, collected from younger SARS patients, also point to additional systemic immunological and inflammatory disorders. Excessive immune responses - in response to COVID-19 infection - can lead to tissue damage and thus to massive impairment of organ function (5, 25, 28). The pronounced disturbances of the cardiovascular system, which also affect organ perfusion and microcirculation, favour the development of 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 pathogenetic 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 myocardial infarction. This was proven in the so-called CAMI-1 study. The safety of the procedure, the efficiency of the CRP adsorber (PentraSorb® CRP), the CRP lowering and the improvement of the cardiological outcome were shown.

According to the data of the clinical CAMI1 study, the elimination of CRP by specific apheresis resulted in a mean reduction of CRP levels by approximately 62% from baseline and a reduction of infarct size by approximately 26%. The significant improvement in cardiac output (LVEF) was 7%. No undesirable effects of CRP apheresis were observed. The ubiquitous molecular patho mechanism of CRP suggests that the tissue protective effect of CRP apheresis also occurs in tissues other than the heart muscle, namely in the lung.

Singular healing trials 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 in these acute and problematic clinical pictures could also be proven (Ries, pers. communication).

CRP apheresis with COVID-19

CRP apheresis is an anti-inflammatory, anti-necrotic 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 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. Patients with severe courses could be intercepted in analogy to the experiences made with patients with acute pancreatitis and SIRS to such an extent that a response to catecholamine administration is ensured and renal complications are prevented.

Apheresis should be performed until a stable reduction of the CRP concentration in the patient's blood below 75 mg/L is achieved.

Especially in case of pneumonia, daily treatment for 3-7 days should be considered. The treatment time is about 5 hours daily, and then the treated plasma volume is about 6000 ml.

Access to the extracorporeal circulation can be peripheral or central. The treatment does not necessarily have to be performed in an intensive care unit.

Target parameters/criteria of the apheresis treatment would therefore be:

- CRP kinetics, permanent reduction of the CRP concentration to <100 mg/L
- Inflammatory biomarkers: IL-1, IL-6, SAA, PCT
- cardiovascular, respiratory and renal SOFA score
- Improvement of the renal function
- Response to vasopressor therapy (substance, maximum daily dose, duration)
- 28 or 60 day mortality rate

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