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Therapeutic Apheresis in COVID-19

DISCLAIMER: *This letter is for informational purposes only and is intended to provide a brief overview of the current scientific and medical information regarding therapeutic apheresis in Covid-19. It is not medical advice and does not replace the judgment or experience of the attending physicians or nurses. The treatment of the patients and the decisions concerning specific patient treatments, including but not limited to the decision whether to use therapeutic apheresis, are the sole responsibility of the attending physicians or healthcare providers. It does also not replace the careful review of the relevant Instruction for Use (IFU) of the respective medical devices used. The IFU of the respective medical advice (including but not limited to the defined time utilization limit and unit maintenance), applicable guidelines and regulations of local authorities, as well as hygienic guidelines applicable in each country, hospital or other facility should always be complied with.*

The SARS-CoV-2 coronavirus provoked a pandemic in the spring of 2020. So far, this has resulted in over 1 million deaths worldwide. An end is not yet in sight. The treatment of the acute phase of the infection is described in the S3 guidelines (Robert Koch-Institute, Berlin). Several extracorporeal therapies in acute COVID are under investigation. It has been reported about removal of virus particles (Schmidt et al., 2021), specific apheresis of C reactive protein (Ringel et al., 2021) and selective apheresis of cytokines (Ruiz-Rodriguez et al., 2021). The coagulation disorders and acute inflammations (hyper-inflammation/cytokine storm) that were feared in spring of 2020 are now mostly well controlled by drugs and intensive care medicine.

The longer the SARS-CoV-2 pandemic lasts, the more scientific papers are published about late symptoms in the context of this coronavirus infection (Andrade et al., 2021). If clinical symptoms persist or recur at least approx. 60 days after the acute infection has been overcome, and this is referred to as long COVID (synonym to late COVID). The spectrum of clinical symptoms is broad and sometimes very weighting or painful for the patients. There is a consensus among the medical community that the long-term clinical disorders cannot be directly attributed to the coronavirus. It is probably the echo of an overactivated immune system, which is not only directed against the virus. Such a phenomenon is known also for other viral infections (Chang et al., 2021; Wirth and Scheibenbogen, 2020).

In the meantime, more than 50 clinical late symptoms have been named (Lopez-Leon et al., 2021), which occur in a wide variety of distribution patterns. According to a meta-analysis, > 80% of approx. 48,000 patients have at least one symptom. The most commonly observed are muscle weakness, chronic fatigue, loss of smell, neurological disorders (“brain fog”), poor memory, tachycardia, joint pain and headache. Treatment is largely based on symptom-related pharmacotherapies that can at least provide relief. These have their limits in the neurological disorders that are similar to Chronic Fatigue Syndrome (CFS).

Late COVID is associated with rheological and immunological changes known from other chronic diseases (Scheibenbogen et al., 2018) that can be measured in blood vessels and plasma. These changes may be corrected by extracorporeal treatments. Two apheresis methods are therefore discussed below. Both double membrane filtration and immunoglobulin adsorption may be suitable for the treatment of long-term clinical disorders associated with a prior SARS-CoV-2 infection, insofar as it is based on disturbances in the micro- and macrocirculation and/or on pathologically relevant autoantibodies.

Double membrane filtration in long COVID

The above symptoms in systemic, vascular or organic clinical manifestations may be based on pathological changes that can be detected in the blood and vessels. It has been reported about

- reduced microcirculation (Østergaard, 2021),
- endotheliopathies (Fogarty et al., 2021),
- increase of plasma concentrations of rheologically and inflammatorily relevant molecules (Proal and VanElzakker, 2021; Pasini et al., 2021),
- microclots in the plasma or on the vessel walls; both in acute and long COVID and the blockage of micro-capillaries (Pretorius et al., 2021).
- formation of neutrophil extracellular traps (NET) that triggers immuno-thrombosis (Ackermann et al., 2021)
- increased blood concentrations of von Willebrand factor (VWF), factor VIII and enhanced coagulation (Wong et al., 2021).

The use of the double membrane filtration may be considered, if such changes in the plasma matrix and the plasma composition are diagnosed in the context of long COVID symptoms.

Immunoadsorption in long COVID

Already at the beginning of the pandemic, the increased risks of humoral autoimmune phenomena were pointed out. The autoantibodies in long COVID are now receiving greater attention worldwide (Khamsi, 2021). In the meantime, a large number of autoantibodies have been described in long COVID, which have different patho-physiological properties. Two aspects deserve particular attention.

After infection, the natural immune defense against SARS-CoV-2 starts through the formation of antibodies against the virus proteins. This can be accompanied by an increased synthesis of autoantibodies against various autoantigens and was observed in ca. 50 % of the patients (Chang et al., 2021). The stronger the antibody production against the virus proteins, the greater was the amount of autoantibodies. Apparently, the formation of autoantibodies is the price that the immune system has to pay for the provision of antibodies against SARS-CoV-2. This virus-triggered autoantibody synthesis is particularly pronounced in COVID (Dotan et al., 2021; Skripuletz et al., 2021).

Another aspect concerns the occurrence of potentially pathologically relevant auto-antibodies. These were identified in a mass screening with approx. 2,800 human extracellular proteins and then tested in mouse models. Some of the autoantibodies were causally involved in the development of disease symptoms (Wang et al., 2021).

In CFS diagnosed in long COVID functional autoantibodies against the β2-adrenoceptor and muscarinic M2 receptor could be detected in 31/31 cases (Wallukat et al., 2021). Autoantibodies against the β2 adrenoceptor are detected also in high prevalence in other diseases like dilated cardiomyopathy, regional pain syndrome and M. Alzheimer. Their occurrence was already known in post infectious CFS (Wirth and Scheibenbogen, 2020). Autoantibodies against phospholipids have also been diagnosed. They are involved in coagulation disorders, and such patients can sometimes develop an anti-phospholipid syndrome (Cristiano et al., 2021).

Autoantibodies against type 1 interferons are diagnosed in a rare but significant number of patients with acute COVID (Bastard et al., 2020). These autoantibodies are directly involved in the virus defense and the antiviral activity of the interferons. The carriers of the anti-interferon antibodies have a high mortality risk because of the defect antiviral defense mechanism.

Experiences with therapeutic apheresis in long COVID

Therapeutic plasma exchange (TPE) was used in patients with acute COVID patients and natural autoantibodies against interferons (de Prost et al., 2021). The virus-toxic effect of interferons was able to unfold again by the removal of the autoantibody containing plasma. It was not possible to assess the clinical impact of this intervention due to the small number of patients studied.

Bornstein et al. (2021) pointed out the option of using apheresis techniques. Approaches are based on the application of lipid apheresis or double membrane filtration which may improve micro-circulation in long COVID patients with endothelial dysfunction and rheological disorders (N.N., 2020).

Immunoadsorption has been used successfully in post infectious Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) to remove autoantibodies against the β2-adrenoceptor (Tölle et al., 2020). In most of the patients a fast improvement of symptoms was observed. Clinical symptoms and the profile of autoantibodies as described with long COVID (Wallukat et al., 2021) are similar to what has been described in post-infectious ME/CFS (Scheibenbogen et al., 2018).

Recently it was shown in an experimental therapy on a patient with long COVID/CFS that the neutralization of these autoantibodies by a single infusion of the DNA aptamer BC007 improves clinical symptoms and micro-circulation within hours and over months (Hohberger et al., 2021). This result has now been confirmed in three other patients with long COVID/CFS (Erlangen University, press release, Sept. 2021). It may be assumed that the removal of autoantibodies against G Protein coupled receptors (GPCR) in long COVID will show similar clinical outcomes and improvements of microcirculation.

Outlook

Clinical trials are recommended to examine if the removal of plasma macromolecules from patients suffering from long COVID/CFS have a positive clinical outcome and an improved micro-circulation. The benefit of removal of autoantibodies against adrenoceptors and other GPCR in diseases like dilated cardiomyopathy is known since more than 20 years (Müller et al., 2000). From the previous experiences in CFS (Scheibenbogen et al., 2018; Tölle et al. 2020) it would be expected that removal of autoantibodies in long COVID improves the clinical features. The diagnostic of autoantibodies esp. against GPCRs in the context of clinical symptoms should be considered.

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