Transfusion and Apheresis Science 61 (2022) 103599

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Immunoadsorption and covid 19 pandemic

Paraskevi Tseke [a,*], Ioannis Griveas [b]

[a] General Hospital of Athens ALEXANDRA, Greece
[b] Army Cher Fund Hospital of Athens, Greece

ARTICLE INFO

Keywords:
SARS-CoV-2
Post covid syndrome
Immunoadsorption columns
Prosorba
Immunoglobins
Apheresis
Plasma

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (COVID-19) pandemic has affected millions of people worldwide. The majority of individuals remain asymptomatic or present with mild symptoms; however nearly 5% of the patients develop severe disease, which is characterized by acute respiratory distress syndrome (ARDS) and multiple-organ failure (MOF) with poor outcomes [1].The basic pathophysiologic mechanism that leads to ARDS and MOF is the exaggerated cytokine release, known as cytokine release syndrome (CRS), or cytokine storm. The initial step is the binding of SARS-CoV2 spike protein to angiotensin-converting enzyme (ACE)− 2 on human cells [2]. After entering the human cells the virus activates inflammation pathways that release pro-inflammatory cytokines and promote cell death by apoptosis with ensuing release of a damage-associated molecular pattern, further amplifying the inflammatory response [3]. Patients with COVID-19 have high levels of inflammatory cytokines, especially interleukin (IL)− 1β, IL-2, IL-6 IL-7, IL-8, IL-9, IL-10, IL-18, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, fibroblast growth factor, macrophage inflammatory protein 1 compared to healthy subjects. Furthermore, the concentrations of IL-6, IL-10, and TNF-α are related to the severity of the disease as it has been seen in patients admitted in intensive care units (ICU). It has been shown that up-regulation of IL-6 may suppress normal T-cell activation, while elevated TNF-α promotes T-cell apoptosis, which consequently may contribute to lymphocytopenia, that has been described in severely ill patients with COVID-19 [4].

At the same time, ACE-2 consumption by viral entry alters angiotensin II (AngII) metabolism, leading to local increase in angiotensin II, which further promotes pro-inflammatory cytokine release and endothelial dysfunction [5].

In the sight of all mentioned above, besides antiviral treatment, which obviously plays significant role in the treatment of COVID-19, immunomodulatory treatments aiming to limit the cytokine storm release or to modulate immune responses seem to be beneficial if timely initiated.

Blood purification techniques and especially selective forms of therapeutic plasma exchange procedures have been reported in many cases in patients with COVID-19. Hemoadsorption with Cytosorb has been more extensively studied, especially in critically ill patients, however to our knowledge there is no clinical experience regarding the use of therapeutic immunoadsorption in COVID-19 patients and there are only sparing evidence that selective immunoadsorption could play an important role in post-covid-19 syndromes.

Immunoadsorption is a therapeutic procedure in which plasma of the patient after separation from the blood is passed through a medical device, which has the capacity to remove immunoglobins, immune complexes or antibodies by binding them to select ligands [6]. Immunoadsorption has been applied in a variety of autoimmune disorders and for desensitization before, or at acute rejection in organ transplantation. Its major advantage over therapeutic plasma aphesis is that it is a selective apheretic procedure, which allows massive removal of autoantibodies, immune complexes and immunoglobins from the first session,

* Correspondence to: Nephrologist General Hospital of Alexandra, Perikleous 26, 17563 Palio Faliro, Greece
E-mail address: tsekedaki@hotmail.com (P. Tseke).

https://doi.org/10.1016/j.transci.2022.103599

Available online 1 November 2022

without affecting other important plasma constituents, for example albumin or coagulation factors and without requiring fluid substitution with plasma, albumin or colloid solutions. Prosorba, the first immunoadsorption comumn that was approved by the FDA in 1987, contained staphylococcal protein A (SPA), which is characterized by its high avidity for the Fc portions of IgG immunoglobins. Ever since, various immunoadsorption columns have been developed using different ligands i.e. SPA, recombinant protein A, sheep polyclonal anti-human antibodies, tryptophan, synthetic oligopeptides, monoclonal mouse antibodies to bind with IgE, specific antibodies for ABO-group antigens and monoclonal camel antibody fragments [7]. In COVID-19 pandemic immunoadsorption procedures have been used or planning to be used in the following clinical conditions:

1. Convalescent plasma donation

Transfusion of plasma units from convalescent donors has been used in the treatment of COVID-19 [8]. However, plasma units contain coagulation factors, albumin and fluids, which can be harmful in some cases, especially in volume overloaded critically ill patients[9,10]. Immunoadsorption has been used in two cases of covalent plasma donors in order to obtain higher antibody concentrates without other plasma components [11]. Rothenburg et al. [11] showed that immunoadsorption could be used to obtain IgG, IgA and IgM immunoglobins and neutralizing Covid antibodies in higher concentrations from convalescent donors. Two donors underwent 7 and 18 cycles of immunoadsorption using Therasorb –Ig flex connected to a LIFE-21 plasmapheresis platform and single needle venipuncture without complications. Following these procedures, tangential flow filtration was performed to concentrate the eluate volumes at least 15-fold, and 1.1 lt of initial eluate volume from the first patient was reduced to 52 ml and 2.7 lt for the second patient was reduced to 61.2 ml of storable antibody concentrate, respectively. Although this seems a promising technique to provide significant concentrates of antibodies and immunoglobins larger studies need to confirm its usefulness and clinical applicability.

2. Extracorporeal supar exctraction to prevent covid-19 associated AKI

The urokinase receptor system is a key regulator of the intersection between inflammation, immunity, and coagulation [12] Soluble urokinase Plasminogen Activator Receptor (SuPAR) is produced by cleavage of uPAR and it is found in various cell types (endothelial cells, activated neutrophils and podocytes) and its circulating levels have been found to corelate with the severity and the outcomes of several infectious diseases and in critically ill patients[13,14]. SuPAR seems to be an independent predictor of the severity and the length of hospital stay in COVID-19 patients, as well[15]. SuPAR is also an immune mediator of kidney damage. High suPAR levels predispose patients to acute kidney injury (AKI) in various clinical settings and especially in critically ill patients with multiple organ failure. A possible mechanism is through alteration of mitochondrial respiration and induction of reactive oxygen series production in proximal tubular cells. A multicenter study in COVID-19 patients revealed that admission suPAR level is a strong predictor of in-hospital AKI, independently of other established risk factors. Patients in the lowest suPAR tertile (<4.60 ng/ml) had a low incidence of AKI (6%), with none of them requiring dialysis, whereas patients in the third tertile (>6.86 ng/ml) had an incidence of AKI of 45.8% with 16.1% requiring dialysis [16].

Miltenyi Biotec has developed a Therasorb suPAR apheresis platform that uses the Life21 Apheresis system for blood withdraw and separation of blood cells from plasma, processing the plasma through a suPAR adsorber for specific extraction of the suPAR protein. This clinical trial will use Miltenyi's Life21 Apheresis and Therasorb platform to treat hospitalized COVID19 patients with high levels of suPAR and without pre-existing kidney injury to determine if the extraction of suPAR prevents COVID19-association AKI.

3. Post covid syndrome

A significant number of patients who have recovered from COVID-19 complain about continuing symptoms even months after the onset of the disease. Chronic fatigue and continuing respiratory problems are the most common symptoms of post COVID-19 syndrome [17]. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an heterogenous syndrome with autoimmune etiology, which is usually triggered by a viral infections and it seems that it has some common symptoms with post or long COVID syndrome [18]. The presence of autoantibodies against M1 acetylcholine receptors [19] and against β1 and β2 adrenergic receptors have been detected in patients with ME/CFS that may contribute to the dysregulation of autonomic sympathetic and parasympathetic nervous system met in such patients[20]. In an observational study in ten patients with post-infectious ME/CFS immunoadsorption with an IgG-binding column for 5 days resulted in a rapid reduction of neurotransmitter receptor antibodies with subsequent clinical improvement in seven patients [21]. Recently, Bornstein et al. [22] reported that in patients with post-COVID-19 fatigue syndrome elevations of neurotransmitter autoantibodies are noted similar to patients in other forms of infection-triggered ME/CFS. In 3 of these patients extracorporeal apheresis (INUSpherese) significantly levels of these autoantibodies and alleviated symptoms of CFS. Accordingly, Kim et al. [23] reported a patient with sensory ataxia after COVID-19 with lesions in MRI suggestive for encephalomyelitis who was succesfully treated with 6 sessions of immunoadsorption.

Although larger studies need to confirm these initial findings immunoadsorption may offer an effective treatment option in patients with ME/CFS or neurological disorders due to long-COVID-19 syndrome.

References

[1] Zhang W, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol 2020;214:108393.
[2] Hoffmann M, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–80. e8.
[3] Tay MZ, et al. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20(6):363–74.
[4] Qin C, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71(15):762–8.
[5] Kuster GM, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020;41(19):1801–3.
[6] Braun N, Risler T. Immunoadsorption as a tool for the immunomodulation of the humoral and cellular immune system in autoimmune disease. Ther Apher 1999;3(3):240–5.
[7] Sanchez AP, Cunard R, Ward DM. The selective therapeutic apheresis procedures. J Clin Apher 2013;28(1):20–9.
[8] Bloch EM, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020;130(6):2757–65.
[9] Xia X, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 2020;136(6):755–9.
[10] Bose S, et al. Medical management of COVID-19: evidence and experience. J Clin Med Res 2020;12(6):329–43.
[11] Rothenburg J, et al. COVID-19 antibody donation using immunoadsorption: report of two cases. Transfus Apher Sci 2021;60(5):103193.
[12] Del Rosso M, et al. The urokinase receptor system, a key regulator at the intersection between inflammation, immunity, and coagulation. Curr Pharm Des 2011;17(19):1924–43.
[13] Huang Q, et al. The diagnostic and prognostic value of suPAR in patients with sepsis: a systematic review and meta-analysis. Shock 2020;53(4):416–25.
[14] Lin MF, et al. Evaluation of the clinical diagnostic value of traditional inflammatory markers and novel biomarkers in intracellular bacterial bloodstream infections. Cytokine 2020;136:155238.
[15] Enocsson H, et al. Soluble urokinase plasminogen activator receptor (suPAR) independently predicts severity and length of hospitalisation in patients with COVID-19. Front Med (Lausanne) 2021;8:791716.
[16] Azam TU, et al. Soluble urokinase receptor (SuPAR) in COVID-19-related AKI. J Am Soc Nephrol 2020;31(11):2725–35.

[17] Alwan NA. Track COVID-19 sickness, not just positive tests and deaths. Nature 2020;584(7820):170.
[18] Long COVID: let patients help define long-lasting COVID symptoms. Nature, 2020. **586**(7828): p. 170.
[19] Tanaka S, et al. Autoantibodies against muscarinic cholinergic receptor in chronic fatigue syndrome. Int J Mol Med 2003;12(2):225–30.
[20] Loebel M, et al. Antibodies to beta adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. Brain Behav Immun 2016;52:32–9.
[21] Scheibenbogen C, et al. Immunoadsorption to remove ss2 adrenergic receptor antibodies in Chronic Fatigue Syndrome CFS/ME. PLoS One 2018;13(3):e0193672.
[22] Bornstein SR, et al. Chronic post-COVID-19 syndrome and chronic fatigue syndrome: Is there a role for extracorporeal apheresis? Mol Psychiatry 2021.
[23] Kim JW, et al. Post-COVID-19 encephalomyelitis. Neurol Res Pr 2021;3(1):18.