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PROSPECTS FOR IMMUNOTHERAPY TREATMENT AGAINST COVID-19 INFECTION

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COVID-19 ინფექციის საწინაღმდეგო იმუნოთერაპიული მკურნალობის პერსპექტივები

ვლ.ბახუტაშვილის სახელობის სამედიცინო ბიოტექნოლოგიის ინსტიტუტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

რეზიუმე

COVID-19 პანდემია დღევანდელი მსოფლიოს მნიშვნელოვან პრობლემას წარმოადგენს. დღესდღეობით არ არსებობს მკურნალობა SARS-CoV2 წინააღმდეგ. ჩვენს ნაშრომში აღვწერთ და ვაანალიზებთ რამდენიმე თერაპიულ პრეპარატს, მოქმედების მექანიზმით, მიმართული იმუნურ სისტემაზე, გამოყენებული COVID-19 სამკურნალოდ, კლინიკურ კვლევებში.

განვიხილავთ იმუნური სისტემის მოდულაციას, 2 ძირითად ასპექტში:

- *პასიური იმუნიტეტის მიღწევა, როგორც პროფილაქტიკა მძიმე და კრიტიკულ პაციენტებში. თანმდევი რისკებით.*
- *ციტოკინების შტორმის დათრგუნვა, რომელიც დაავადების მძიმე და კრიტიკული ფორმის მთავარი გამომწვევი მიზეზია.*

საბოლოოდ აშშ წამლის სააგენტოს თანახმად, განიხილავენ მონონუკლეარულ ანტისხეულებს პასიური იმუნური პასუხის მისაღებად და დექსამეტაზონს ციტოკინების შტორმის დასათრგუნად, პრეპარატის შეყვანის დროის გაკონტროლებით, დაავადების სტადიის მიუხედავად.

COVID-19 pandemic is a real threat for the people worldwide. Currently there is no specific treatment to eliminate SARS-CoV2 from the infected humans. In this review we describe and analyze several therapeutical preparations, which target immune system, used in the clinical trials to treat COVID-19. We discuss immune system modulation in two main aspects:

- first, achievement of passive immunity as prophylactic of severe and critical disease in SARS-CoV-2 infected people with concomitant risks;
- second, inhibition of cytokine storm, which is main cause of severe and critical disease.

Finally, according to the USA NIH guidelines, monoclonal antibodies for passive immunity and dexamethasone for cytokine storm are discussed with emphasis on the timing of administration concerning COVID-19 patients' stage of disease.

Passive Immunity

Neutralizing antibody production by the immune system is triggered to interrupt initial interaction between the SARS-CoV-2 spike protein and the human ACE2 receptor and subsequent cellular uptake of the virus (1,2). The immune response kinetics, magnitude, and its casuality with disease severity during acute-phase response have been defined extensively. SARS-CoV-2 elicits humoral and cellular immune responses; within 7 days of infection, virus-specific memory CD4+ and CD8+ T cells emerge, peaking within 2 weeks but remaining detectable at comparatively lower levels for ≥100 days. Simultaneously, there are strong B-cell responses with immunoglobulin M (IgM) and IgA antibodies detected by days 5–7 and IgG antibodies by days 7–10(3). The magnitude of both antibody and T-cell responses is not uniform among individuals with COVID-19 and appears to be influenced by disease severity (4,5). In patients with first contact with the new viral antigen enhancing concentration of antibodies in blood by infusion of plasma from convalescent individuals or synthesized monoclonal antibodies could benefit the course of disease. These opportunities were tested in several clinical trials.

Convalescent Plasma (CP)

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the

inflammatory response (6). The use of CP involves transfusing plasma collected from patients who have already recovered from an illness, in an attempt to transfer neutralizing antibodies and confer passive immunity (7,8). The potential efficacy of CP was first described during the Spanish influenza pandemic of the early 1900s (9). Since then, CP has been used to attempt to treat a wide range of viral infections, including measles, parvovirus B19, H1N1, Ebola and some coronaviruses (10).

In the Pandemic of Covid-19, plasma therapy has been used for treating COVID-9 patients (11). In an initial study, five patients with COVID-19 with ARDS* underwent plasma therapy and clinical outcomes were compared before and after CP transfusion. The results showed improvement in the patients' clinical condition. In a study by Duan et al. in ten severe adult cases, the results showed that a dose of 200 mL CP was well tolerated and could significantly increase or maintain neutralizing antibodies at a desirable level. This treatment was capable of reducing viremia within 7 days. After the application of this treatment method, clinical and paraclinical symptoms improved rapidly within 3 days. Radiological studies also showed varying degrees of absorption of lung lesions within 7 days. According to these observations, CP can be expected as a life-saving option in patients with severe COVID-19 (12).

On 24 March 2020, the US FDA announced the approval of convalescent plasma therapy for critically ill individuals with COVID-19 as an emergency investigational new drug (13). Obviously, CP should be used on the initial stages of COVID-19 to help eliminate viral particles from the patients and prevent massive invasion of virus in the tissue. During the severe and terminal stages CP will not benefit patients as the course of disease is driven by mechanisms which involve immune overreaction and hyper-inflammation, which are not prevented by specific antiviral antibodies from CP.

Anti SARS-CoV-2 monoclonal antibodies (MaB)

Bamlanivimab (Elly Lilly) and the combination of casirivimab plus imdevimab (Regeneron Pharmaceuticals) are anti-SARS-CoV-2 monoclonal antibodies (anti Spike virus protein) available through US FDA Emergency Use Authorizations (EUAs) for the treatment of outpatients with mild to moderate COVID-19 who are high risk for progressing to severe disease and/or hospitalization.

Bamlanivimab was authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes those who are 65 years of age or older, or who have certain chronic medical conditions.

Clinical trials are continued but there are promising positive clinical results for Banlavinimab and Casirivimab plus Imdevimab (14,15). An interim analysis of this study suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19 who received the antibody infusion a median of 4 days after symptom onset (16).

Casirivimab plus imdevimab for outpatients with mild to moderate COVID-19 who received an infusion of the drug combination a median of 3 days after symptom onset (17).

Inhibition of immune response

Cytokine storm as the hallmark of ARDS, is an uncontrolled systemic inflammatory response triggered by some immune system cells due to the release of proinflammatory cytokines and chemokines. In this regard, high expression levels of cytokines and chemokines, including IL1-β, IL1RA, IL7, IL8, IL9, IL10, FGF2, GC-SF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGFB, TNF-α, and VEGFA are observed in the serum of patients with COVID-1(18). Inability of the immune system to control this condition has led to the death of many patients with COVID-19(19). Consequently, attenuating cytokine storm in patients with COVID-19 is one of the goal of hospital therapy.

Therapeutic Management of Patients with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of the following:

- Dexamethasone (or other corticosteroids) with or without remdesivir
- Baricitinib with remdesivir.

* ARDS - acute respiratory distress syndrome

Corticosteroids

Dexamethasone have been studied in critically ill patients with ARDS with conflicting results (20,21,22). Seven randomized controlled trials that included a total of 851 patients evaluated use of corticosteroids in patients with ARDS. A meta-analysis of these trial results demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and duration of mechanical ventilation (mean difference, -4.93 days; 95% CI, -7.81 to -2.06 days) (23,24).

Finally, Recommendations on the use of corticosteroids for COVID-19 are largely based on data from the "RECOVERY" trial, a large, multicenter, randomized, open-label trial performed in the United Kingdom (25). This trial compared hospitalized patients who received up to 10 days of dexamethasone to those who received the standard of care. Mortality at 28 days was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care. This benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment. It should be emphasized that this study also found no benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment.

Due to wide availability and low-price dexamethasone is the best recommended and effective choice of COVID-19 patient treatment of (Table 1).

Baricitinib (Br)

The kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (26).

Baricitinib, sold under the brand name Olumiant, is a drug for the treatment of rheumatoid arthritis (RA) in adults whose disease was not well controlled using RA medications called tumor necrosis factor (TNF) antagonists, Br is an inhibitor of Janus kinase an important enzyme in the mechanics of inflammation (27,28).

The Panel's recommendations for the use of baricitinib are based on data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2), a multinational, randomized, placebo-controlled trial of baricitinib use in hospitalized patients with COVID-19 pneumonia. Participants (n = 1,033) were randomized 1:1 to oral baricitinib 4 mg or placebo, for up to 14 days, in combination with intravenous (IV) remdesivir, for up to 10 days. Participants who received baricitinib had a shorter time to clinical recovery than those who received placebo (median recovery time of 7 vs. 8 days, respectively). This treatment effect was most pronounced among those who required high-flow oxygen or non-invasive ventilation but were not on invasive mechanical ventilation. The difference in mortality between the treatment groups was not statistically significant (29).

Other Janus kinase (Ruxolitinib(30), Tofacitinib[Noclinical trials to date]) as well as Bruton's Tyrosine kinase inhibitors were used or proposed to do so to treat cytokine storm in COVID-19 patients, but only Br has some recommendations from US NIH as others have very limited clinical data.

Interleukin inhibitors

Interleukin (IL)-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the severe acute respiratory syndrome-associated coronavirus (SARS-CoV) induces a dose-dependent production of IL-6 from bronchial epithelial cells (31).

Preliminary, unpublished data from randomized, controlled trials failed to demonstrate efficacy of sarilumab or tocilizumab in patients with COVID-19. There are only limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19(32).

Small one center published trial is available for tocilizumab (33) Treatment of patients with COVID-19 through tocilizumab therapy, some laboratory parameters including C-reactive protein (CRP) and IL-6 concentrations should be assessed before and after tocilizumab therapy. In addition, tocilizumab was used along with methylprednisolone in some patients with COVID-19. The studies have shown that the level of IL-6 decreased in patients after taking tocilizumab, while the level of IL-6 increased significantly in patients who were not treated with tocilizumab. TCZ appears to be an effective

treatment option in patients with COVID-19 at high risk of cytokine storm. More studies needed to evaluate definite clinical benefits of the drug.

Vitamin D

Immunoregulatory role of Vitamin D (VD) is well known (34). VD was evaluated as a supplement to COVID-19 patients' diet, especially in obese cohort (35,36). Combined to obesity VD deficiency hypothesized as a cause of severe symptoms of COVID-19 (37). Indeed, VD deficiency or insufficiency, defined as 25(OH) D below 20 ng/mL and 30 ng/mL respectively were associated with an increased risk of SARS-CoV-2 (38). Moreover, very low vitamin D levels appear to be associated with greater risk for admission to an intensive care unit (ICU) and consequent mortality (50%) (39,40,41). Few randomized clinical studies are published up to date with positive (42) and negative results (43) and further studies are needed to evaluate VD's effect in COVID-19.

There is some evidence that VD deficiency is associated with hypocalcemia, which is observed in COVID-19 patients and could serve as a potentially useful biomarker for disease severity and outcome in patients with SARS-CoV-2 infection (44,45,46). Therefore, vitamin D supplementation might have a therapeutic role in these patients.

In our opinion would be reasonable to recommend a goal of VD blood levels >30 ng/mL. at least to those who are at particularly high risk such as older men with co-morbidities such as diabetes and obesity.

Finally, recommendations and treatment guidelines from USA NIH are most balanced guide for the treatment of COVID 19 patients (Table 1).

Table 1. NIH basic COVID-19 treatment guidelines

Disease severity	NIH Panel's treatment recommendation
Not hospitalized. Mild to Moderate COVID-19.	SARS-CoV-2 neutralizing antibodies for the patients with high risk of disease progression. Bamlanivimab (Elly Lilly) and the combination of casirivimab plus imdevimab (Regeneron Pharmaceuticals).
Hospitalized but does not require Oxygen supplementation.	Remdesevir could be appropriate. Pannel recommends against dexamethasone or other corticosteroids administration at this stage.
Hospitalized and required noninvasive Oxygen supplementation.	Use one of the following options: • Remdesevir for patient who require minimal oxygen dose • Dexamethasine + Remdesevir for patients with increasing amounts of oxygen • Dexamethasone alone when Remdesevir is not available or couldn't be used for patients with increasing amounts of oxygen
Hospitalized and required invasive Oxygen supplementation.	Dexamethasone only

Further clinical and experimental studies are necessary to improve clinical care of COVID-19 patients.

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SUMMARY

COVID-19 pandemic is a real threat for the people worldwide. Currently there is no specific treatment to eliminate SARS-CoV2 from the infected humans. In this review we describe and analyze several therapeutical preparations, which target immune system, used in the clinical trials to treat COVID-19. We discuss immune system modulation in two main aspects: first, achievement of passive immunity as prophylactic of severe and critical disease in SARS-CoV-2 infected people with concomitant risks; and, second, inhibition of cytokine storm, which is main cause of severe and critical disease. Finally, according to the USA NIH guidelines, monoclonal antibodies for passive immunity and dexamethasone for cytokine storm are discussed with emphasis on the timing of administration concerning COVID-19 patients' stage of disease.

Keywords: Covid-19, immunotherapy, prospects