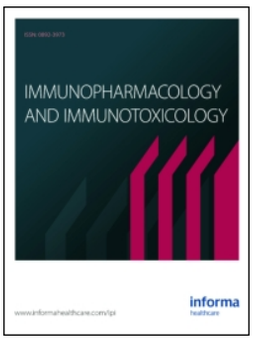

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REVIEW ARTICLE

Future perspective: biologic agents in patients with severe COVID-19

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ABSTRACT

The SARS-CoV-2 is a β-CoV, which is enveloped by non-segmented positive-stranded RNA virüs. When β-CoV infects the respiratory tract, it can cause mild and/or severe acute respiratory syndrome (SARS) with consequent release of cytokines/mediators, including interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-10, IP10, IL-12, IL-13, IL-17, IL-33, IL-25, IL-37, IL-38, GCSF, GM-CSF, HGF, IP-10, MCP-1, MIP-1α (also known as CCL3), IFN-γ, IFN-α, TRAIL, MCSF, and TNF-α. Our hypothesis of writing this article can be summarized as; if the monoclonal antibody (mAb) administered by us does not inhibit the immune response for the β-CoV and inhibits uncontrolled-adaptive/hyperimmune responses (also called cytokine storm) on endothelium level, then it may cause severe coronavirus disease 2019 (COVID-19). Anakinra is a human IL-1 receptor antagonist. By inhibiting IL-1α/IL-1β competitively from binding to the IL-1 type-I receptor, anakinra, neutralizes the activity that pertains to these key mediators of autoinflammatory and/or immune processes. Tocilizumab is a blocker of IL-6R that can effectively block IL-6 signal transduction pathway. Omalizumab that binds to the CH3 domain is near to the binding site for the high-affinity IgE Fc receptors type-I of human IgE. Myocardial, lung and hepatorenal injury in patients with COVID-19 could be due to cytokine storm, hypoxic injury, or/and direct endothelial/vascular injury. We propose combination of mAbs with remdesivir and/or favipiravir in severe COVID-19 cases, such as septic shock, acute respiratory deficiency syndrome, and/or multiple organ failure. Finally, we highlight the therapeutic mAbs that target patients with severe COVID-19.

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Origin of SARS-CoV-2

On 31 December 2019, a cluster of pneumonia cases, caused by a newly identified β-coronavirus (β-CoV), occurred in Wuhan. CoVs are divided into four genera (α-CoV, β − CoV, γ− CoV, and δ-CoV). World Health Organization (WHO) officially named the disease as coronavirus disease 2019 (COVID-19) and Coronavirus Study Group (CSG) of the International Committee proposed name as the new coronavirus Severe Acute Respiratory Syndrome (SARS)-CoV2, both issued on 11 February 2020 [1–4]. The sudden emergence and rapid spread of SARS-CoV2 are threatening global health [1–6].

The SARS-CoV-2 is a β-CoV, which is enveloped by non-segmented positive-stranded RNA virus [6]. No clear data is available revealing the extent and duration of the exposure of the host immune response to the virus leading to failure. Six CoVs have been identified as human-susceptible virus, among which α-CoVs HCoV-229E and HCoV-NL63, and β-CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, causing moderate pulmonary symptoms similar to a common cold, respectively. α- and β-CoV are able to infect mammals. γ- and δ-CoV tend to infect birds [2–7]. The other two known β-CoVs, SARS-CoV and MERS-CoV cause severe infections (Mild to moderate (mild symptoms up to mild pneumonia): 81%, Severe (dyspnea, hypoxia, or >50% lung involvement on imaging): 14%, Critical (respiratory failure, shock, or multi-organ system dysfunction): 5%) [7,8].

Recent studies determined the crystal structure of the SARS-CoV-2 receptor-binding domain (RBD) (engineered to facilitate crystallization) in complex with hACE2. They show that RaTG13, a bat coronavirus closely related to SARS-CoV-2, also uses hACE2 as its receptor. The differences among SARS-CoV-2, SARS-CoV, and RaTG13 in hACE2 recognition shed light on potential animal-to-human transmission of SARS-CoV-2 [7]. ACE inhibitors and ARBs increase the expression of angiotensin-converting enzyme 2 (ACE2). Angiotensin receptor blockers (ARBs) and ACE inhibitors may increase the mortality risk of COVID-19 severity (septic shock, acute respiratory deficiency syndrome, or multiple organ failure). There is no data available concerning the possibility of reinfection with SARS-CoV-2 after recovery from COVID-19. Viral RNA shedding declines with resolution of symptoms, and may continue for days to weeks [8]. In the experimental model conducted 5 years ago, the researchers have interpreted the failure of response of the treatment as follows; evaluation of available SARS-based immune-therapeutic and prophylactic modalities revealed poor efficacy; both monoclonal antibody (mAb) and vaccine approaches failed to

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neutralize and protect from infection with CoVs using the novel spike protein [9]. It has been argued here that the mAb treatments were inconclusive. We review the literature on COVID-19 immünopathophysiology, its interaction with target self-cells and the acquired immune response to the β-CoV. Our hypothesis of writing this article can be summarized as such; if the humanized mAb administered by us does not inhibit the immune response for the β-CoV and inhibits uncontrolled adaptive hyperimmune responses (proinflammatory cytokines/procoagulant proteins) on endothelium level, then it may cause severe coronavirus disease 2019 (COVID-19) cases.

Host immune response and immunohistopathology

The immune mechanism is vital for the control of CoV infections, while it can also lead to immunohistopathogenesis, associated with the hyper immune response out of control. β-CoV can activate innate and adaptive hyperimmune responses. When β-CoV (subgenus sarbecovirus, Orthocoronavirinae subfamily) infect the respiratory tract it can cause mild or SARS with consequent release of pleiotropic/anti-inflammatory cytokines/mediators, including interleukin (IL)-1β, IL-2, IL-4, IL-5,IL-6, IL-7,IL-8, IL-10, IL-12, IL-13, IL-17, IL-33, IL-25, IL-37, IL-38, CD40L, CXCR3, GCSF,HGF,IP-10, MCP-1, MIP-1α (also known as CCL3), IFN-γ, TRAIL, MCSF, and TNF-α [10]. Innate immunity is needed in a precise regulation to eliminate the β-CoV, otherwise will result in immunohistopathology.

The binding of β-CoV to the Toll-Like Receptor (TLR3, TLR7, TLR8, and TLR9 sense viral RNA and DNA in the endosome (The viral RNA receptor RIG-I) causes the release of pro-IL-1β which is cleaved by caspase-1, followed by inflammasome activation and production of active mature IL-1β which is a mediator of fever, respiratory tract inflammation [11]. Interesting therapeutic alternative that was previously explored with influenza virüs (IF) is to target cellular TLR4 with specific mAb therapies. TLR4-null mice were highly resistant to infection by the mouse-adapted IF A virüs [12]. The IL-1 family member (IL-1F) of cytokines plays a critical role in the regulation of metabolic inflammation, particularly by pro-inflammatory members IL-1α and IL-1β. In contrast, the IL-1 receptor antagonist (also called Anakinra, recombinant IL-1Ra), also a member of the IL-1F, represents an endogenous mechanism to reduce IL-1–driven inflammation [7–10]. Anakinra is a human IL-1 receptor antagonist. By inhibiting IL-1α and IL-1β competitively from binding to the IL-1 type I receptor, anakinra neutralizes the activity that pertains to these key mediators of autoinflammatory and/or immune processes [11]. TLR7 is produced in innate immune cells which recognize β-CoV by promoting the production of antibodies against the β-CoV and the generation of pro-inflammatory/pleiotropic cytokines including IL-6 and IL-1F. The X chromosome influences the immune system by acting on many other proteins, including TLR8, CD40L, and CXCR3 which can be over-produced in women, and influence the response to β-CoV infections and vaccinations. Moreover, the biallelic expression of the X-linked genes can promote harmful autoimmune/inflammatory responses.

IL-37 and IL-10 have the ability to suppress innate and acquired immune response. IL-37 has the capacity to inhibit severe proinflammation by acting on IL-18Rα receptor. IL-37 and IL-10 perform its immunosuppressive activity by acting on mTOR and increasing the AMP kinase. IL-37 inhibits MHC class II and inflammation in autoinflammatory/metabolic syndromes (obesity, rheumatologic autoimmune diseases, …, etc.) by suppressing MyD88 and subsequently IL-1β, TNF-α, IL-6, and CCL2. The suppression of IL-1β by IL-37 in inflammatory state induced by β-CoV can have a new therapeutic effect [11].

Another inhibitory cytokine is IL-38, the cytokine of the IL-1F. IL-38 is produced in several tissues/immune cells, such as B cells, macrophages, placenta, brain, and heart. It is involved in a wide variety of diseases, including chronic inflammatory rheumatologic diseases. IL-38 is a potential therapeutic inhibitory cytokine which inhibits proinflammation in viral infections including that caused by β-CoV, providing therapeutic strategy [7–10].

Biologics in patients with severe COVID-19

We aim combination of anti-cytokine mAbs with remdesivir or favipiravir in severe COVID-19. Specifically, we highlight the implications of specific features of the COVID-19 for promising immune-therapeutic interventions that could target the β-CoV or the uncontrolled adaptive uncontrolled-hyperimmune response. We discuss how studies focused on the dysfunctional host immune response will be crucial in informing the development of immune-therapeutic humanized mAbs.

Humanized anti-IL-6 receptor (anti-IL-6R) monoclonal antibody

When we review that IL-6 is a pleiotropic cytokine (IL-6 is synthetized by cells of the innate immune arm, such as neutrophils and monocytes) with a proinflammatory activity affecting both the innate and the adaptive immune system and IL-6's pathway, we see the correlation with the coagulation proteins (Figure 1). Furthermore, how the direct association with the coagulation protein has positive or negative effect on the regulation of the coagulopathy in severe patients infected with β-CoV has not been clarified.

Tocilizumab (Anti-IL-6R, Roactemra®) is a blocker of IL-6R that can effectively block IL-6 signal transduction pathway. Tocilizumab is currently used for rheumatoid arthritis (RA), but its efficacy has been demonstrated also anti-PD-1/PD-L1 or anti-CTLA-4 immune checkpoint inhibitors against (ICI)-induced immune/cyto-related adverse events (ICRAE), starting from the rationale of an ICI-induced systemic inflammatory response syndrome similar to cytokine release syndrome (CRS) [13]. Moreover, along with the improvements in symptoms related to systemic inflammatory response syndrome, some authors reported a clinical improvement in other ICRAE with tocilizumab used in patients with cancer with

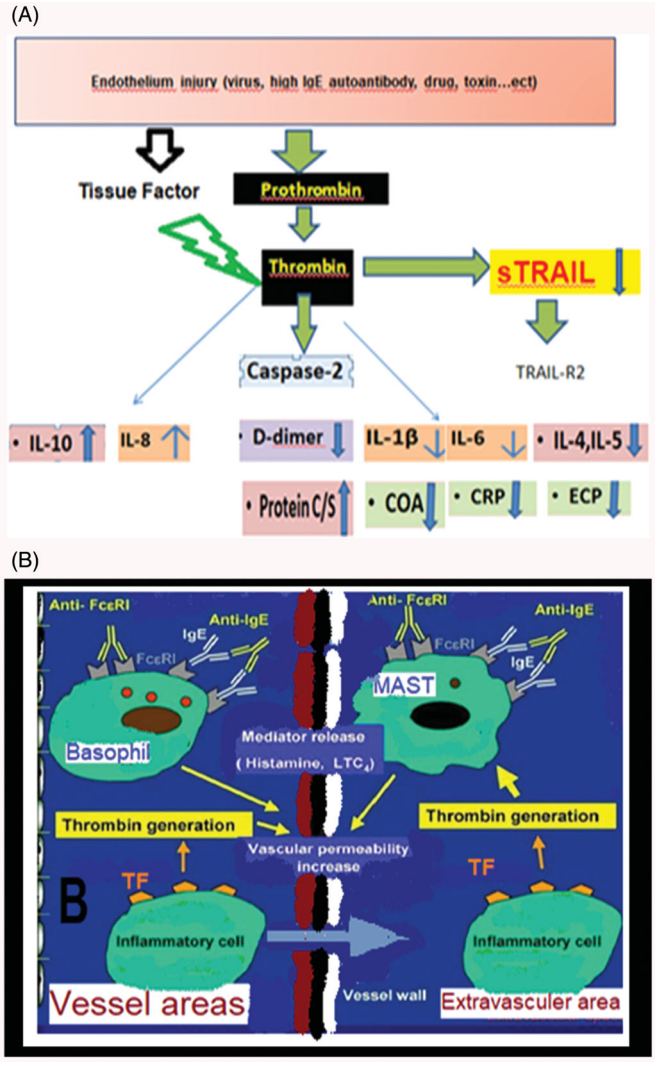

Figure 1. (A) Omalizumab Effects on some biomarkers. In our previous studies, we showed that after Omalizumab (also called AntiIgE) therapy protein C/S, IL-10, and IL-8 increases and D-Dimer, STRAIL, COA, IL-1, IL-6, IL-4, IL-5, ECP, and CRP levels decreases. ECP: eosinophil cationic protein; CRP: C-reactive protein; IL: interleukin; sTRAIL: soluble tumor necrosis factor-related apoptosis-inducing ligand; COA: ceruloplasmin oxidase activity; TF: tissue faktör; Anti-IgE: omalizumab. (B) Omalizumab Effects on vascular and extravascular areas.

immune-related toxicity from anti-PD-1 agents [13–15]. Uncontrolled and retrospective trial conducted on 20 patients with severe COVID-19 disease and high IL-6 levels has yielded preliminary and encouraging outcomes [16]. A trial has been initiated in Italy on patients with COVID-19 and high IL-6 levels.

IL-6 levels both in the serum (ranging from 5 to 200 pg/mL, with 1–16 pg/mL being the physiologic range in healthy people) and in the synovial fluid (about 100–1000 fold higher than controls) [17]. No clear data is available in the literature with respect to the transition of the virus to the synovial fluids in the COVID-19 sepsis. If the virus causes synovial inflammation, then it can be anticipated that this biological agent can be effective in those areas. No conclusive data are available in the literature whether or not the direct inhibition of IL-6 in receptor or serum triggers the virus replication.

Other target molecules that can be used for the inhibition of IL-6 are Kevzara® (sarilumab: The mAb to IL-6Rα) [17] and Sylvant® (siltuximab: The human-mouse chimeric immunoglobulin G1κ mAb against human IL-6) developed for idiopathic multicentric Castleman's disease [18]. Modulating autophagy, promoting the production of other immunity effector mechanisms and antimicrobial/anti-inflammatory cytokine and/or mediators and not inhibiting the mechanism of the host to repair the damaged tissues are the aspects aimed by this treatment protocols.

Human IL-1 receptor antagonist

Anakinra is a human IL-1 receptor antagonist. By inhibiting IL-1α and IL-1β competitively from binding to the IL-1 type I receptor, anakinra, neutralizes the activity that pertains to these key mediators of autoinflammatory and/or immune processes [11,19]. From the five clinical trials performed, and given the unfeasibility of developing new studies of anakinra in RA, it may be concluded that site injection reactions, infections at higher doses (>100 mg), and immunogenicity are the most frequent adverse events related to anakinra administration [19]. In the view of the role of IL-1 regulation in the coagulation, the medication can be considered as the first plan on the increased IL-1 levels in patients with Severe COVID-19, however, the effect on the viral replication has not been indicated and furthermore, a safety issue exists. Suppression of pro- IL-1Fs and IL-6 have been shown to have a therapeutic effect in many inflammatory diseases, including viral infections. Biologic agents such as tocilizumab (also called Anti-IL6) (Rx dose: 162 mg SC every week, Actemra) and Anakinra (also called Anti-IL1), the effect on Anti Thrombin III, Protein C, Protein S, D-Dimer levels and in severe cases coursing with coagulopathy is not clear. Whether or not aggravatıng the cytokıne storm ın cases wıth sepsis remains also unclear.

Anti-IgE humanized monoclonal antibody

The development of anti-IgE therapy (omalizumab, Xolair) over the past 30 years provides an interesting example of the emergence of a conceptually new therapeutical class for severe persistent allergic asthma (SPA) and chronic idiopathic urticaria (IgE independent urticaria) (CIU). It is conceivable that mast cells residing in the nasal lining, other areas of the mucosal tracts, and in the skin, differ in tryptase and chymase content, sensitivity, receptor regulation, and life span. Omalizumab (also called anti-IgE humanized mAb) that binds to the CH3 domain, is near to the binding site for the high-affinity IgE Fc receptors type-I (also called FcεRI) of human IgE. It can neutralize IgE and inhibit the IgE-mediated allergic/immunologic pathway without sensitizing cells and has been approved for therapeutic use in both adults and children [20–30].

We have revealed in the trials previously performed by us that the response of B lymphocytes in patients with allergic, non-allergic, autoimmune/genetic (such as Behçet's disease, CIU, Netherton, severe asthma with coagulopathy) depending and/or not depending on the serum IgE level are regulated on numerous mediators [20–30]. The facts that

omalizumab has established its safety profile and it has no serious side effect have led us to perform these trials. When administered to the patients with hepatic cirrhosis and asthma, we have experienced that it has not distorted the coagulation proteins and liver function tests [22,25,29]. When toxic epidermal necrolysis (TEN) was developed in diabetic patients with high mortality risk, we have used instead of intravenous immunoglobulin (IVIG) and has received a similar successful clinical response [29]. The principal problem in β-CoV infection is the Viremia and the overresponse to the Viremia. In consideration of the facts that we have administered omalizumab in patients with sepsis without encountering any side effects and it safely decreases the coagulant proteins (D-Dimer) [20,22,25,26,28] and proinflammatory cytokines/mediators (IL-1β,-4,-5,-6,-17,-33), macrophages and mast cells (MCs), ceruloplasmin oxidase, MDA, H2O2, CRP, TRAIL), increases the anti-coagulant proteins (protein C, S) [22], we could anticipate that we may administer it for severe COVID-19. Increase of ferritin, CRP and D-Dimer in patients with severe Covid-19 is directly associated with the mortality.

Omalizumab's adjuvant effect on serum IL-8 does not create any issues in severe asthma cases with bronchiectasis, however, it indirectly reduced the serum IL-6, IL-1β, CRP levels in these cases. The pulmonary functional test (FEV1, FVC, PEF, and FEV1/FVC) values were compared before and after omalizumab treatment. In the clinical responders, there was a significant increase seen in FEV1 and FVC [21]. Therefore, we contemplate that omalizumab could contribute I *n* terms of respiratory functions when ARDS is developed in severe phase of Covid-19 disease. In case, the patients do not experience sepsis condition and the fever response does not occur and, therefore, WBC, lymphocyte, and neutrophil levels in their serum start to decrease accordingly, it could be anticipated not to have any effect. Trials are urgently required to be performed in this regard. Recent study showed that in children with severe or moderate asthma, treatment with anti-IgE (also called omalizumab) decreased the duration of Rhinovirus (RV) infections/illness, viral shedding, and the risk of RV infections. Additionally, direct evidence that blocking FcεRI decreases susceptibility to RV infections [31].

Study from Hong Kong reported that β-CoV shedding may begin 2–3 d before the appearance of the first symptoms. Additionally, COVID-19 control measures should be adjusted to account for probable substantial presymptomatic transmission [32]. Another study from the UK showed that β-CoV, influenza (IF) viruses, and RV in exhaled breath and coughs of children and adults ends with acute respiratory diseases. Surgical face masks significantly reduced detection of IF virus RNA in respiratory droplets and β-CoV RNA in aerosols, with a trend toward reduced detection of β-CoV RNA in respiratory droplets. They suggested that surgical face masks could prevent transmission of β-CoV and IF viruses from symptomatic patients [33]. IF viruses and RV cause ∼80% of allergic asthma exacerbations in children and adults [34], with RV being the most frequent, cause up to 70% of virally induced asthma exacerbations. mAbs such as omalizumab inhibit T Helper 2 immunity reduce asthma exacerbations, which are mainly due to viral infections, when added to inhaled corticosteroids (ICS) in patients with severe allergic asthma [34]. Interestingly, the underlying mechanism for this unexpected beneficial effect of omalizumab appears to be related to the fact that plasmacytoid dendritic cells (PDC), which produce large quantities of IFN-α, express FcεRI on the mast cell surface [34–36]. Another research from Australia reported that uncontrolled SPA is associated with impaired antiviral immune responses. Authors determined if treatment with omalizumab resulted in improvement in antiviral innate immune responses to IF and/or RV. Response was assessed by ELISA with release of interferon (IFN)-α, IFN-λ, IFN-γ, IL-6, IL-10, IL-5, and IL-13. At baseline visit subjects with severe allergic asthma compared to healthy controls demonstrated impaired IFN-α, and IFN-λ release in response to IF and RV. In the clinical responders, there was a significant increase in IFN-α, and IFN-λ to IF and a trend toward improvement to RV. Patient with SPA demonstrates impaired systemic innate immune responses to IF and RV. Treatment with omalizumab, which results in SPA control is associated with improvement in innate antiviral responses [37–40]. Protection against IF disease was achieved by targeting TLR4 with small molecule antagonists, like TAK-242, or with anti-TLR4-specific mAbs. Indeed, targeting a cellular protein would overcome the drawbacks associated with virus or β-CoV genetic heterogeneity [12,40–42].

Myocardial/lung and hepatorenal injury in patients with COVID-19 could be due to cytokine storm, hypoxic injury, or direct endothelial/vascular injury [39]. Cardiovascular diseases are more frequent in males and people without cardiovascular dysfunctions infected by β-CoV have a better prognosis, but these effects are still under study. In addition, considering the clinical studies evaluating biological inhibitors, the aforementioned dual mechanism hypothesis is clinically testable, and future trials in the field and experimental β-CoV challenge model should specifically examine the effects of T helper 2 and/or mast cell inhibitors on viral and other respiratory infections, β-CoV clearance, and (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IP10, IL-12, IL-13, IL-17, IL-33, IL-25, IL-37, IL-38, GCSF, GM-CSF, HGF, IP-10, MCP-1, MIP-1α, CD40L, CXCR3 (also known as CCL3) [38,43], IFN-γ, IFN-α, TRAIL, MCSF, TNF-α, and responses, as well as on the treatment and prevention of β-CoV induced re-infections in patients with COVID-19. ACE2 is located on the X chromosome. COVID-19 shows a difference in severity/fatality rate between males (2.8%) and females (1.7% [44]. The sex hormones have different immunoregulatory functions, which could influence immune protection or autoimmune/inflammatory disease severity [45]. Studies suggest that there are many differences between men and women in the immune response to COVID-19 and autoinflammatory diseases.

A clinical study of the anti-IL-6 mAbs therapy sarilumab [46] is also being tested for its efficacy. Other clinical studies are also testing the effects of GM-CSF, including the use of gimsilumab [47], lenzilumab [48], and namilumab [49]. A theoretical possibility is that the suppression of inflammation by IL-6 antagonism might delay viral clearance. However, IL-6 blockade also results in rapid reduction of serum IL-10, an

immunosuppressive cytokine secreted by macrophages, which may mitigate concerns about prolonging viral clearance [50]. Many antiviral and anti-cytokine monoclonal antibodies are currently available for severe COVID-19, to be used alone or in combination, either at the initial disease stage or to protect patients from a cytokine relaseinflammatory syndrome, preventing ARDS [51]. In some cases, anti-IL6 mAb therapy was successful in stabilizing the alveolar-capillary membrane and preventing/reversing ARDS [52]. Specifically, nanomedicine studies may provide clues on chloroquine-induced alterations of SARSCoV-2 cellular uptake [53].

Lommatzsch et al. [54] showed that a case with SPA treated with anti-IgE (omalizumab) has no evidence of an allergic persistent asthma exacerbation, loss of asthma control, or pneumonia during COVID19 disease. They suggested the underlying SPA or the antibody used for omalizumab, or both, might have exerted protective effects. Several SARS-CoV-2 monoclonal antibodies are poised to enter clinical trials [55].

It is a high probability for the antiviral medications to prevent the worsening condition of mild COVID-19 diseases. Other adjuvant strategies are required for severe COVID-19 with critical condition and liver function tests, D-Dimer and Blood Proinflammatory cytokine/mediator levels gradually increasing and progressing toward acute respiratory distress syndrome (ARDS). The effect of the disease on coagulation proteins in the patients with severe COVID-19 has not yet been clarified. It has further not been observed in the literature whether it has positive or negative effect on mean platelet volume (substantial in thrombosis), Anti Trombin III, Protein C, Protein S, and D-Dimer and whether or not it increases the viral replication. Furthermore, the effect of β-CoV on antinuclear antibody (ANA), autoantibodies/anti-neutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigens, anti-double-stranded DNA, rheumatoid factor (RF), intermediate filament antibodies (IMF) in the Host immune system has not been indicated in the literature. Kawasaki's illness is an autoinflammatory/autoimmune condition, which affects children. In the COVID-19 period, β-CoV infection aggravates the condition of Kawasaki disease, but it has also been noted that children affected by SARS-V-2 may develop a disease similar to Kawasaki's disease. However, it is uncertain whether the β-CoV alone can give Kawasaki illness-like forms. As in COVID-19, Kawasaki's disease and its similar forms are mediated by pro-inflammatory/pro-coagulant cytokines produced by cells such as MCs. In light of above, it is therefore pertinent to think that by blocking pro-inflammatory cytokines with new anti-proinflammatory molecules, such as IL-37, IL-38, and IL-10, it is possible to alleviate the symptoms of the disease and have a new available therapeutic tool. Ronconi et al. suggested that since Kawasaki and Kawasaki-like diseases present immunodeficiency, treatment with immune-modulator/anti-inflammatory molecules must be applied very carefully [56]. Conti et al. [57] suggested new anti-viral therapies with new drugs should also be taken into consideration. For instance, microbes are known to bind TLR, inducing IL-1, a pleiotropic cytokine, highly proinflammatory, mediator of fever and fibrosis. In addition, Conti and Younes [58] strongly believe that the levels of activation of the immune cells are higher in women than in men, and it is correlated with the trigger of TLR7 and the production of IFN. TLR7 is higher in women than in men and its biallelic expression leads to hyperimmune uncontrolled responses and increases the resistance to β-CoV infections. However, the production of pro-inflammatory IL-6 [20] after β-CoV infection is lower in women than in men and is often correlated with a better longevity. In addition, on the X chromosome there are loci that code for the genes involved in the regulation of immune cells such as FOXP3, and transcription factor for Treg involved in β-CoV immunohistopathogenesis. Gender differentiation is contraversial in mAb therapies in severe COVID-19. Is there any difference between genders in therapies, duration, dosages and side effects in severe COVID-19? We will evaluate these questions in the future.

In conclusion, this mini review provides a summary of mAb therapeutic compounds that showed potential in fighting severe COVID-19. No physiological data is available in the literature indicating that the β-CoV binds on the airborne pollen and particulates in air and water due to the thermal and/or wind effect and accordingly whether the mucosal adsorption increases or not. The correlation between the increase of the β-CoV amount on exposure and the cytokine release storm at the breaking point of the immune-response occurring has not yet been clarified. Corticosteroids (also called dexamethasone) could be given together with the natural flavonoid luteolin because of its anti-inflammatory properties, especially its ability to inhibit MCs, which are the main source of proinflamatory-cytokines ((IL)-1β, IL-37, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IP10, IL-12, IL-13, IL-17, TNF) in the lungs [10,59–61]. The concern we have is how the β-CoV evolves. Further mutations, and how that putatively could bypass immunity in the future. We propose combination of mAbs with remdesivir and/or favipiravir in severe COVID-19, such as septic shock, acute respiratory distress syndrome and/or multiple organ failure. Finally, we highlight the therapeutic mAbs that target in patient with severe COVID-19. We strongly believe that all these devices described above can lead to greater survival.

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Disclosure statement

The authors declare that they have no conflicts of interest.

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