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Derleme / Review

IMMUNOGENOMIC APPROACH TO THE CLINICAL MANAGEMENT OF COVID-19 SYNDROME

COVID-19 SENDROMUNUN KLİNİK YÖNETİMİNDE İMMUNOGENOMİK YAKLAŞIM

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ÖZET

SARS-CoV-2 enfeksiyonu sonucu gelişen ve "COVID-19 sendromu" olarak tanımlanabilecek tablonun üç özel immünogenomik gelişim aşaması vardır; başlatıcı, ilerleyici ve komplikasyon fazları. Her COVID-19 fazı, farklı terapötik klinik müdahaleler gerektiren kritik patobiyolojik korelasyonlara sahiptir. Renin-anjiyotensin sistemi (RAS) genleri, koronavirüs ailesi üyelerinin neden olduğu enfeksiyonların başlaması için gereklidir ve SARS-CoV-2 enfeksiyonunu takiben kritik immün gen ürünleriyle, özellikle de IFN ailesinin üyeleri ile güçlü bir etkileşime sahiptir. Bu makale, COVID-19 immün sendromu olarak tanımlanabilecek multisistemik tablonun klinikopatolojik seyrine ilişkin daha önce yayınladığımız üç aşamalı modelin kavramları çerçevesinde COVID-19 için tedavi protokollerini güncel bir yaklaşımla gözden geçirmeyi amaçlamaktadır. Mevcut tedavi seçeneklerinin RAS'ı etkileyen gelecekteki olası terapötik adayları da sendromun immünogenomik perspektifiyle ele alınmaktadır.

Anahtar Kelimeler: COVID-19, remdesivir, paxlovid, coronavirus, covid-19 tedavisi.

ABSTRACT

The COVID-19 syndrome following the SARS-CoV-2 infection has three unique immunogenomic disease development phases; initiating, propagating, and complicating. Each COVID-19 phase has critical pathobiological correlations requiring distinct therapeutic clinical interventions. Renin-angiotensin system (RAS) genes are essential for initiating infections caused by coronavirus family members and may have a strong association with the exchange of critical immune genes, particularly IFN-family, in due course following the SARS-CoV-2 infection. This paper aims to review therapeutic protocols for COVID-19 within the concepts of our previously published three-phase model regarding the clinicopathological course of COVID-19 immune syndrome. The current treatment options have been reviewed in this synopsis within our three-phase disease schedule. Possible future drug candidates affecting the RAS are also considered from the immunogenomical perspective of the syndrome.

Keywords: COVID-19, remdesivir, paxlovid, coronavirus, covid-19 treatment.

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INTRODUCTION AND COVID-19 IMMUNE SYNDROME

COVID-19 (Coronavirus Disease 2019) immune syndrome could take place following the viral pandemic infection of beta coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) (1). The clinical spectrum of SARS-CoV-2 manifestations ranges from asymptomatic infection or mild respiratory tract symptoms to severe pneumonia leading to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Then, SARS-CoV-2 viral infection could trigger exaggerated or impaired immune responses with uncontrolled immune attacks on the target human tissues leading to the COVID-19 immune syndrome (2). The genome sequencing and phylogenic studies revealed that SARS-CoV-2 is classified under the same subgenus of the previous severe acute respiratory syndrome virus (SARS-CoV) but within a different clade. The structure of the receptor-binding gene region is very similar to the SARS-CoV, and both viruses utilize the same receptor, angiotensin-converting enzyme 2 (ACE2), for cell entry and disease development (3).

COVID-19 syndrome can manifest itself with a wide variety of multi-systemic involvements. Extrapulmonary manifestations include thrombosis, myocarditis, acute renal injury, gastrointestinal mucositis, hepatocellular injury, hyperglycemia, ketoacidosis, vasculitis, neurological stroke, ocular disorders, and dermatologic complications. Local paracrine, autocrine, and intracrine tissue-based renin-angiotensin system (RAS) containing ACE2 in the lung and multiple extrapulmonary tissues could participate in the genesis of COVID-19 (4). Likewise, endothelial injury, vascular thrombosis, uncontrolled immune responses, vasculitis, and maladaptation of the ACE2-associated RAS pathways can complicate multi-systemic manifestations of COVID-19 (5).

We have recently indicated that several RAS genes are critical for initiating the infections caused by coronavirus family members and may have a strong association with the exchange of immune genes, particularly interferon (IFN)-family, in due course following the SARS infections (6). COVID-19 syndrome following the SARS-CoV-2 infection has three unique immunogenomic disease development stages, namely "initiating", "propagating", and "complicating" phases. Every disease phase of COVID-19 has unique characteristics of clinical manifestation in association with the different genomic mechanism(s), which mainly include RAS (7). Moreover, each of the three COVID-19 phases has critical pathobiological correlations requiring specific therapeutic clinical interventions. Our group describes the three disease phases as "asymptomatic/pre-symptomatic phase", "respiratory phase with mild/moderate/severe symptoms" and "multi-systemic clinical syndrome with impaired/exaggerated or defective immunity" (7). We had proposed that ACE2 and ANPEP transcripts are drivers of the 'initial phase' whereas EGFR and IGF2R transcripts are active in the 'propagating phase'(8). In addition, the interferon (IFN) and immune system-related genes are suggested to have a significant role in the 'complicating phase' (7). This paper aims to review therapeutic protocols of COVID-19 within the concepts of our previously published three-phase model (6, 7) regarding the clinicopathological course of COVID-19 immune syndrome.

SARS-CoV-2 is mainly transferred in humans via respiratory droplets through face-to-face contact. The virus can be transferred among asymptomatic, pre-symptomatic, and symptomatic human beings. The average time from the contact to the beginning of characteristic symptoms is around five days. Most (97.5%) of the affected people develop the disease symptoms within 11.5 days (9). The main symptoms of COVID-19 are fever, dry cough, and shortness of breath. Currently, the diagnosis of COVID-19 is dependent upon polymerase chain reaction (PCR) tests. However, false-negative PCR tests were detected in 20% to 67% of the patients. Current treatment protocols for COVID-19 include the best available practices of the supportive measures of acute hypoxic respiratory failure complicated within the late stages of the syndrome. The case-mortality rate for COVID-19 differs significantly by age, ranging from 0.3 deaths per 1000 cases among cases aged 5 to 17 years to 304.9 deaths per 1000 cases among patients aged 85 years or older (9). During the intensive care unit, patient mortality may be up to 40% (9).

The viral pandemic spread rapidly, and global prevention strategies failed to prevent the virus from becoming a health disaster. COVID-19 has already caused the mortality of hundreds of thousands of people, and the numbers are increasing (10). The clinical course of COVID-19 could differ in distinct countries. The US, Brazil, and India have the highest cases, whereas some countries have encountered less documented cases (10). Our country, Turkey, is one of the most infected with SARS-CoV-2. However, the death toll in Turkey is prominently lower than expected (10). The COVID-19 situation in Turkey is officially controlled with periodically updated standardized management protocols, and the outcome is publicly reported by the Ministry of Health (MOH). Turkey has truly been admired from an international perspective for its performance in controlling of COVID-19 pandemic. The Turkish MOH scientific COVID-19 board published guidelines for managing the syndrome. The effective algorithm for COVID-19 testing in Turkey is depicted in Figure 1. The management of COVID-19 patients all over Turkey has been performed according to these guidelines and official recommendations.

The current COVID-19 treatment options within the essential concepts of Turkish MOH (11) have been reviewed in this synopsis within our recently published three-phase disease schedule (6). In addition, possible future drug candidates affecting the RAS are also considered from the immunogenomical perspective of the syndrome.

It seems rational to develop and implement various clinical management strategies based on the three described phases (initial phase, propagating phase, and complicating phase) in the development of COVID-19. The immunogenomic features of each disease phase are distinct from each other, leading to different clinical outcomes. Therefore, it is consequential to focus on these phases separately (6). It is essential to thoroughly understand the

unique three stages of the disease in order to develop a robust treatment strategy for the COVID-19 syndrome. Treatment strategies that can be effective in each phase are discussed in the following sections of the review.

TREATMENT STRATEGIES FOR COVID-19 PHASE I (INITIATING PHASE)

In this phase of COVID-19, the disease is either asymptomatic or pre-symptomatic. If the disease is pre-symptomatic, there are mainly two forms of disease which are; respiratory and intestinal forms. In this initiation phase, ACE and Aminopeptidase N (ANPEP) genes play essential roles in the development of the disease (7). Members of the coronavirus family SARS-CoV and SARS-CoV-2 strains use the ACE2 receptor at the initial stage of cell adhesion and penetration to enter the cell (12). Numerous studies indicated that COVID-19 patients differ in ACE2 expressions if they have a secondary disorder such as diabetes, hypertension, or cardiovascular diseases (13-15). ACE2 and ANPEP transcripts are the driver molecules for the development of infection at the initial stage and function as auxiliary receptors. ANPEP is a member of an enzyme family that plays a role in the final digestion of peptides produced by hydrolysis of specific proteins by gastric and pancreatic proteases, expressed in many different tissues in the human body, such as the kidney and lung (16). ANPEP functions in many intracellular pathways and has previously been reported to act as a receptor for human coronavirus 229E / HCoV-229E and cytomegalovirus (16). ANPEP exhibits similar expression patterns with the ACE2 receptor in a wide variety of human tissues (17).

Current Treatment Strategies

After the physical examinations and laboratory or imaging workups, the general management issues for a patient in the initiating phase include empiric treatment for bacterial pneumonia in select patients and prevention of and evaluation for venous thromboembolism (18). There are several potential treatment agents which may be administered in this initial phase.

Clinicobiological Perspectives for Hydroxychloroquine/ chloroquine

There are ongoing trials evaluating the clinical efficacy of these drugs. To summarize, the studies can be classified into three groups. The first group of authors proposes that hydroxychloroquine is effective against COVID-19. In in vitro studies, both chloroquine and hydroxychloroquine were shown to inhibit SARS-CoV-2, and this effect was found to be more potent with hydroxychloroquine (19). In a French study, it was shown that chloroquine derivatives are effective in improving clinical and virological outcomes, but more importantly, it reduces mortality in COVID-19 (20). In the Turkish COVID-19 guidelines, hydroxychloroquine is given with a dose of 2x200 mg per oral for five days in COVID-19 patients who are not complicated or who have mild pneumonia (11). We think that this type of usage of hydroxychloroquine is appropriate according to the COVID-19 disease phases because it directly targets the first (initiating) phase of the disease, which we think hydroxychloroquine exerts its best potential. The second group of data favors that hydroxychloroquine is effective against COVID-19. Preliminary data from a recent study reported that hydroxychloroquine did not appear to have a benefit for hospitalized patients(21). The World Health Organization ended the hydroxychloroquine arm of its large SOLIDARITY trial, citing a lack of mortality benefit based on its preliminary data (22). In an observational study with nearly 1400 patients, hydroxychloroquine use was reported in 811 patients and was associated with a higher risk of intubation or death (23). The reason why hydroxychloroquine was found to be ineffective in these patients can be the COVID-19 unique phases. These data are driven by hospitalized patients who are probably in the second or third phase of COVID-19. We think that the effect of hydroxychloroquine is more evident, especially in the initiating phase of the disease. In June 2020, the US FDA canceled its emergency use authorization for hydroxychloroquine in patients with severe COVID-19, mentioning that the known benefits no longer outweighed the known and potential risks (24). The third group of data stands between the last two groups and favors uncertainty. These studies suggest that the efficacy of hydroxychloroquine in the treatment of COVID-19 is uncertain (25, 26).

The use of these drugs prevents glycosylation of ACE2 by inhibiting terminal glycosylation of ACE2, the receptor targeted by SARS-CoV and SARS-CoV-2 for cell entry. Therefore, ACE2 can interact less effectively interact with the SARS-CoV-2 spike protein. It is anticipated that this may even lead to inhibition of viral entry in progressive conditions (27, 28). However, the mechanism of action of both the hydroxychloroquine drug and the chloroquine drug against the disease is not yet fully comprehended. On the other hand, according to some research at the molecular level, hydroxychloroquine and chloroquine have the ability to limit the proper functioning of lysosomes and autophagy. These drugs are classified as weak bases by considering the basal side chains in their molecular structure and structure. Thanks to their weak basic properties, these drugs accumulate in the compartments located in the cell. More specifically, hydroxychloroquine and chloroquine accumulate in the lysosomal compartments with passive entry into the cells. The accumulation of hydroxychloroquine and chloroquine in lysosomes causes an increase in pH level. Thanks to this elevation, this elevation limits the functionality of lysosomal enzymes (29, 30). The weakened functionality blocks the main histocompatibility complex (MHC) class II, which plays a vital role in the antigen communication of cells, causing damage to antigen communication. Damaged MHC complex and antigen communication can reduce the effect of both autoimmune T cells and inflammatory response by triggering the use of

mechanisms with low affinity. These changes can also affect the function of autophagy by blocking the fusion occurred between autophagosomes and lysosomes (29-32).

In addition to molecular-level studies, activities of hydroxychloroquine and chloroquine drugs are related to the activation of immunity. They could diminish the production of cytokines as well as the signaling of toll-like receptors (29). The utilized drugs can accumulate in the endosomes as well as in the lysosome. Similarly, it prevents the activity of the Toll-like receptor (TLR) signal by altering the pH level in the endosomes. Notably, the TLR7 receptor cannot incorporate with RNA, which is the specific ligand of TLR7, as well as TLR9 receptor, cannot bind with its specific ligand, DNA, and this situation leads to a weakening of the signal pathway. In addition, the production of cytokines, such as IL-1 and IL-6, has been observed to decrease as a cellular effect of this treatment. The main reason for this is that the TLR signal plays a significant role in cytokine production, and the decrease in the affinity of Toll-like receptors with the utilization of these two drugs triggers the decrease in the production of inflammatory cytokines (29-32).

According to some crucial research, hydroxychloroquine and chloroquine drugs have an essential role in the immune response. Thanks to their passive entry into cells and accumulation in specific locations, their mechanisms of action could reduce the functionality of their signaling pathways and receptors, which are central to the immunometabolism and natural immune response. First of all, autophagy is highly critical for the immune response of cells against foreign invaders (31, 33). In light of the studies conducted, autophagy is known to regulate interferon production. As a result of in vitro studies, it has been illuminated that the use of hydroxychloroquine and chloroquine drugs down-regulates expression levels of IFN-induced genes encoding RNA and DNA-sensing receptors. This reduces the production of interferons, which play a vital role as the first line of defense against infections with down-regulation, specifically type 1 IFN (31, 34, 35). Furthermore, the inhibition of antigen communication via MHC-II also affects the immune response of these drugs. Drugs entering the cells lead to an increment in the pH level of the environment in direct correlation to their mechanism of action thereby disrupting the proper function of antigen production. Along with the damage to antigen production, activation of T cells, which is important for the immune response, is also damaged in direct proportion. As a result of research, the mechanism of action of hydroxychloroquine and chloroquine drugs may have the ability to slow down the progression of SARS-CoV-2 infection by triggering both the activation of the immune system and the decrease in inflammation, as predicted in HIV infection(36, 37).

In addition to the immune response genes, hydroxychloroquine and chloroquine are also associated with RAS genes (38). RAS genes regulate autophagy flow in cells. According to the researches, RAS genes and the RAS pathway, which is correlated with these genes, have been demonstrated to make important contributions in both negatively and positively affecting autophagy. The direction of this effect is determined depending on the cell type and properties. In the study conducted by Du et al., it was observed that the expression level decreased in the RAS signaling pathway in the cell administered with the use of the hydroxychloroquine drug. As an outcome of hydroxychloroquine, called an autophagy inhibitor, RAS expression level could decline, and hence, autophagy inhibition is regulated. Conducted and ongoing studies reveal that hydroxychloroquine and chloroquine drugs may function in relation to RAS genes (38-40).

Clinicobiological Perspectives for Favipiravir

Favipiravir is an RNA polymerase inhibitor. It was previously used for influenza treatment. Now it is used in COVID-19, and there are promising results in recent studies. In a study of COVID-19 patients with non-severe disease, favipiravir was related to faster rates of viral clearance and more frequent radiographic improvement compared with lopinavir-ritonavir (41). In the Turkish treatment guides, favipiravir was given with a dose of 2 x 1600 mg loading dosage and then 2 x 600 mg maintenance dosage in uncomplicated patients, patients with mild and severe pneumonia, and patients who progress under hydroxychloroquine treatment (11). Therefore, Turkish guides offer favipiravir in all phases of COVID-19.

Favipiravir is a drug produced against the virus, especially the influenza virus. The mechanism of action of this drug mainly relies on the inhibition of RNA-dependent RNA polymerase that belongs to the RNA virus. Blockage of the RNA-dependent RNA polymerase may also prevent the propagation of virus numbers by prohibiting the viral genome from replicating. The favipiravir drug must be in activated form to perform the inhibition function, and phosphorylation in the cell helps the favipiravir to switch to the activated form. A great deal of studies demonstrate that the strength of the anti-viral effect of favipiravir drug can be changed with the aid of the addition of purine nucleic acids (42-44).

Favipiravir treatment is applied to patients against the inflammatory response produced by the cells against viral replication, which begins with the entry of the virus into the cells. Therefore, there is a link between the favipiravir drug and the immune response genes. In light of the studies, it has been concluded that the load applied by the virus to the host cells would decrease with the use of the favipiravir drug, and with this reduced load, the severity of the disease caused by the virus infection and in addition, the immunosuppressive effect may be reduced. Moreover, initiating favipiravir treatment in the early stages can provide a more potent defense mechanism against the virus by providing effective activation of both immune response genes (45, 46).

Clinicobiological Perspectives for Azithromycin

Azithromycin is generally used in combination with hydroxychloroquine, and this treatment is no longer suggested by some authors because both agents prolong QTc (47). On the other hand, some authors propose that hydroxychloroquine+azithromycin has been widely misrepresented in both clinical reports and public media. Evidence about the use of hydroxychloroquine alone or of hydroxychloroquine+azithromycin in inpatients is irrelevant concerning the efficacy of the pair in early high-risk outpatient disease. The authors outlined that five studies, including two controlled clinical trials, have confirmed significant outpatient treatment efficacy (48). Therefore, hydroxychloroquine+azithromycin treatment may be beneficial in patients who are in phase 1 of COVID-19 infection.

Azithromycin is an antibacterial drug used primarily in respiratory infections. It is a member of the macrolide group due to the fact that azithromycin contains the lactone ring. This drug binds to the 23S rRNA belonging to the 50S ribosomal subunit of the invader, which enters the host cell. After incorporation, it prevents the protein synthesis of an invader. The inhibition of protein synthesis occurred as a result of the misleading transpeptidation and translocation steps. Additionally, the binding of azithromycin could prevent the 50S ribosomal subunit. According to the research, azithromycin, which functions as a macrolide, can even function as an anti-viral other than its antibiotic property. Thanks to its anti-viral activity, it can reduce susceptibility to virus infection. Azithromycin's anti-viral and anti-inflammatory properties could change the level of cytokine expression (49, 50).

Azithromycin has an effect on immune response genes thanks to its ability to change cytokine levels and interferon expression. According to the results of the research, it is observed that the level of cytokine expression decreased as a result of azithromycin treatment. This decrease is especially seen in TNFα and IL-1β expressions. Alteration can lead to a stronger immune response by supplying enough number memory of T cells. Besides, azithromycin up-regulates the expression of interferon. This significant increase is observed, especially in interferon-β and interferon-λ levels. With the aid of these changes, the activity of the virus so as to weaken the host cell can be declined, and on the other hand, a stronger immune response can be given (49, 51-53).

Clinicobiological Perspectives for Lopinavir-Ritonavir

These protease inhibitors are used for HIV, but their effect remains lower than expected in SARS-CoV-2. In a study with 199 patients with severe COVID-19, the addition of lopinavir-ritonavir (400/100 mg) twice daily for 14 days to standard care did not decrease the time to clinical improvement (54). As a result of this study, it can be suggested that the use of lopinavir-ritonavir is not effective in the third phase of COVID-19. The use of these drugs may be beneficial in special subgroups. In the Turkish treatment guides, lopinavir-ritonavir is suggested for pregnant patients with a dose of 400/100 mg BID for 10-14 days (11).

Lopinavir and ritonavir drugs are generally used in combination with each other. Lopinavir is an anti-viral drug. Lopinavir has the ability to mimic the peptide bond that has been potentially attacked by the virus entering the host cell. On the other hand, ritonavir is a protease inhibitor as well as is likely to inhibit enzymes involved in lopinavir metabolism. The presence of ritonavir drug in lopinavir metabolism increases the lopinavir effect and functionality. Therefore, the combined use of these two drugs results in a stronger immune response to the virus infection and a weakening of the virus's spread in the host cell. It is also envisaged in studies that this inhibition mechanism can stop the replication that the SARS-CoV-2 virus has accompanied by the host cell (55, 56).

Lopinavir and ritonavir drugs have an important role in immune response genes. According to the studies, with the use of these drugs, IL-8 expression, which is significant for the immune response, may cause induction. This induction is also important for the NF-κB signal pathway. It has been shown that increased IL-8 expression has a strong contribution to the formation of an innate immune response after the host is infected by the virus. It was observed that activation of the NF-κB pathway, which is important for the immune response targeted to be induced, with varying IL-8 expression levels was triggered. By activating this signaling pathway, it is aimed to protect host cells by creating an innate immune response against infection by causing changes in the expression of inflammatory genes such as chemokine and cytokine (57, 58).

The study conducted by Boccara et al. suggests that using lopinavir and ritonavir drugs together may be related to renin-angiotensin system (RAS) genes. Accordingly, it has been found that the combination of the two drugs may cause the activation of the RAS by up-regulating the angiotensin II type-1 receptor (AT1R). The activation of RAS increases the expression of angiotensinogen mRNA (59). These changes are thought to contribute to the strengthening of the defenses of host cells.

Clinicobiological Perspectives for Remdesivir

Remdesivir is a novel nucleotide analog, and its activity against severe SARS-CoV-2 is demonstrated in vitro (54). It is generally offered for patients who are in the third phase of COVID-19. Remdesivir also did not appear to reduce time to recovery among patients with mild-moderate disease (60), indicating that remdesivir is not effective in phase 1-2 COVID-19 patients. On the other hand, a study from China with 237 patients with severe COVID-19 reported that time to clinical improvement was not statistically different with remdesivir compared with placebo (54). Its side effects include nausea, vomiting, and transaminase elevations, and sometimes could be severe enough to stop the treatment (54).

Remdesivir, which is used as an important potential treatment in SARS-CoV-2 infection, aims to prevent the activity of RNA polymerase. The nucleotide analog, remdesivir, binds to RNA and prevents nucleotide binding. Failure to add more nucleotides to the RNA transcription chain supports stopping RNA transcription in progress. As a result of the studies performed, the chance of inhibition of virus replication, including SARS-CoV-2 virus, increases as a result of remdesivir treatment (61, 62).

Clinicobiological Perspectives for Molnupiravir

Molnupiravir is a nucleoside analog prodrug with antiviral efficacy against some RNA viruses, including influenza viruses and SARS-CoV-2. It is metabolized to the pharmacologically active form called ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe, and its incorporation into viral RNA by the viral RNA polymerase results in errors in the viral genome leading to inhibition of replication.

The evidence of the use of molnupiravir mostly relies on the randomized controlled phase 3 study “MOVe-OUT”(63). It was conducted with 775 non-hospitalized patients with mild to moderate COVID-19 who have risk factors of progression to severe COVID-19 and/or hospitalization. The risk of hospitalization or death was reduced by 6.8 percent due to molnupiravir treatment (about a 50% relative risk reduction). Based on these results, 100 ort he treatment of mild-to-moderate COVID-19 in adults with positive direct SARS-CoV-2 viral testing who are at high risk of progressing to severe COVID-19, and for whom alternative COVID-19 treatment options are not readily available or clinically appropriate, the US FDA has issued an Emergency Use Authorization (EUA) 100ort he molnupiravir use(64).

Based on the mechanisms and clinical data mentioned earlier, it can be said that molnupiravir may be effective in the 1st and 2nd phases of the disease, where viral replication is rapid. Consistent with this, molnupiravir has been shown to be ineffective in the later stages of the disease(65).

Another point of interest with molnupiravir is the issue of mutagenicity. Due to its mechanism, there is a concern that the drug may cause variant changes as a result of non-lethal mutations in the 100ort . Although based on controversial study designs and non-standard methods, some authors have stated that genotoxicity can also 100ort in host cells and that nucleoside analog drugs should be examined 100ort he possibility of genotoxicity in all study phases(66).

Clinicobiological Perspectives for Paxlovid® (Nirmatrelvir/ ritonavir)

Paxlovid® is a novel oral antiviral drug, given for five consecutive days to patients with mild to moderate diseases, with similar high-risk settings as molnupiravir. Paxlovid® consists of nirmatrelvir, a main protease 100ort he100r of 3Clpro of SARS-CoV-2, and ritonavir (inhibits cytochrome P450 3A4, so causes nirmatrelvir metabolism to slow down and keeps high serum levels). The US FDA has issued an EUA 100ort he emergency use of Paxlovid® in adults and pediatric patients (12 years of age or older).

The EUA of the drug is mainly based on the phase 2/3 EPIC-HR study(67). 100ort he primary endpoint, the relative risk reduction in the modified intention-to-treat analysis population for Paxlovid® compared to placebo was 88% (95% CI: 75%, 94%). In a study of population-based real-world data from 4737 patients treated with this drug, Paxlovid® use was associated with a significant decrease in the rate of severe COVID-19 or mortality with adjusted HR 0.54 (95% CI, 0.39-0.75)(68).

One of the concerns with the use of nirmatrelvir/ritonavir is that a rebound of COVID-19 occurs soon after in patients receiving treatment(67). This brings to mind the possibility of drug resistance through mutations in the 3Clpro or cleavage genes. Although this situation is not very rare, it was seen in the phase 2/3 study at similar rates to those in the placebo group (23 of 990 patients, 2.3% in the nirmatrelvir–ritonavir group, and in 17 of 980, 1.7% in the placebo group). In addition, similar rebound rates were observed in patients using molnupiravir compared to patients using Paxlovid®, indicating that this situation, which did not differ significantly from placebo, was not also unique to Paxlovid®(69).

Clinicobiological Perspectives for Dexamethasone

In a recent study, it was proposed that oral or intravenous dexamethasone reduced 28-day mortality among hospitalized COVID-19 patients compared with usual care alone (70). It is stated that corticosteroids may modulate immune-mediated lung injury and reduce progression to respiratory failure and death. Moreover, no benefit was seen among patients who did not require either oxygen or ventilator support. It can be suggested that dexamethasone is effective in the third phase of COVID-19.

The main mechanism of action of the dexamethasone drug occurs as an anti-inflammatory. Dexamethasone belongs to the corticosteroid group. Therefore, dexamethasone can bind to the glucocorticoid receptor, causing a change in targeted gene expression. In addition, glucocorticoids can block the apoptosis of neutrophils and the function of the NF-κB signaling pathway, which are critical in the immune system. As a result of the changes, dexamethasone functions as an anti-inflammatory molecule (71).

The dexamethasone drug utilized against infection plays a key role in the immune response. As a result of the use of this drug, there is a significant increase in the level of cytotoxic T-lymphocyte antigen 4 (CTLA-4). With this increase, a decline is observed in the differentiation as well as an increase of naïve T cells. Thanks to the down-regulation of CTLA-4 expression and proper regulation of specific T cell numbers, which contribute to the strengthening of the cells, the elevation of IFNγ level is detected. These expression level changes help to delay the death of infected cells as well as ensure the longevity of the cells. However, the time of administration of dexamethasone

treatment plays a very critical role in triggering an immune response against infection (71, 72).

In addition, dexamethasone therapy is associated with RAS genes. As a result of research and experiments, effects on the expression of RAS genes were observed in cells treated with dexamethasone. After that, angiotensin-converting enzyme (ACE) activity significantly increased. The increase in ACE activity is a precursor to a more effective response to the resulting infection. This change in the level of expression could prevent the invader from propagating in the cell 101 ort he 101 reduce its number by inducing the potential defense mechanism against the foreigner entering the host cell (73-75).

Clinicobiological Perspectives for Tocilizumab

Tocilizumab is an IL-6 receptor 101 ort he 101 r. It is commonly used for rheumatic diseases and cytokine release syndrome. Recently it has been investigated in randomized trials 101ort he treatment of COVID-19. In a recent study with severe COVID-19 patients who had laboratory results favoring a pro-inflammatory and pro-thrombotic state, no significant adverse events were thought to be directly related to tocilizumab. And it was related to a decrease in C-reactive protein, D-dimer, and ferritin levels (76). It can be suggested that tocilizumab is effective in the third phase of the disease and in the case of an impaired immune system with a macrophage activation syndrome.

Another drug used against SARS-CoV-2 infection, tocilizumab, can inhibit the interleukin-6 (IL-6) receptor. IL-6 is a cytokine produced by cells that are important 101ort he immune system, such as B and T cells, and in addition, it has the ability to regulate its inflammatory response. Tocilizumab associates with the soluble membrane that binds to the IL-6 receptor. This binding can inhibit the IL-6 receptor and stop the inflammation regulated by IL-6 (77).

Treatment of tocilizumab contributes to the immune response by significantly changing it. IL-6 expression level is essential 101ort he immune response developed against infection. This cytokine, B-lymphocytes, and T-lymphocytes, which are the critical parts of the immune system, have strong communication. Tocilizumab may limit the expression of the IL-6 cytokine. Thanks to the IL-6 antagonist, the reduced IL-6 function has the potential to relieve mortality from infection (78).

The drug Tocilizumab inhibits IL-6 expression, which is part of the immune response. IL-6 expression may vary depending on the JAK / STAT and RAS pathway. Therefore, IL-6 activation or up-regulation leads to indirect activation in the RAS pathway. The decrease in the IL-6 level causes it not to be activated properly in the RAS pathway. In this context, studies can 101 ort the changes caused by tocilizumab treatment in effects on RAS expression (79).

Clinicobiological Perspectives for Interferon Beta

In a recent study with primarily non-severe COVID-19, patients were randomly assigned to a combination intervention versus control. Patients who received interferon beta as part of the intervention in the intervention group had more rapid times to a negative SARS-CoV-2 reverse transcription polymerase chain reaction test on a nasopharyngeal swab, clinical improvement, and hospital discharge (80). In this study, the patients who had phase 1-2 COVID-19 infection were included. Another recent clinical study suggested that the administration of IFN-a2b drug during the early stages of COVID-19 may lead to favorable clinical responses (81). On the other hand, IFN genes have a role in all phases of infection. Future studies that will focus on the relationship between IFN genes and interferon beta treatment will help to clarify this association.

The interferon beta has an important role in the treatment of SARS-CoV. This drug binds to type 1 interferon receptors such as IFNAR1 and functions on the JAK/STAT signaling pathway of a critical immune response. Interferon beta has the potential to suppress the inflammatory response resulting from infection. This suppression can 101 ort depending on the anti-inflammatory cytokine, B-cell, and T-cell levels (82, 83).

The immune response is affected due to interferon beta used for therapeutic purposes. Activation of T-cells, one of the essential elements of the immune response, is prevented by the interferon beta drug. Changes in the activation of T cells cause apoptosis of these cells, reducing the number of T cells. However, MHC II decreases in line with improper activation of T cells. As a result, thanks to interferon beta, the effectiveness of the function of natural immune genes is increased (82, 84).

Interferon is involved in the expression and function of beta RAS genes. Research shows that RAS expression can be specifically down-regulated as a result of interferon beta therapy. This anticipated expression reduction strengthens the host's defense mechanism by having the potential to slow down cell growth. Thanks to the strengthened defense mechanism, the survival rate of the patients increases, and the time to fight foreigners increases at a similar rate (85, 86).

II-B. Future treatment strategies with drug candidates

From our point of view, future treatments should focus on the pathobiological development mechanisms of COVID-19. The three-phase approach and the unique genetic properties in each phase have essential importance. In the 101ort he101re, it was stated that ACE2 is a receptor of entry of SARS-CoV-2 into the host cells, and its increase has been implicated in increased susceptibility of individuals to this infection. The clinical course of COVID-19 proposes a role of ACE2 blockade, rather than its overexpression, in causing the pathogenesis (87). Blocking the RAS results in up-regulation of ACE2, attenuating acute respiratory syndrome and myocarditis in COVID-19-infected cases. Conversely, an increase in ACE2 expression may facilitate 101ort h to the host of COVID-19, worsening the clinical course (88). The relationship between SARS-CoV-2 and ACE2 is demonstrated in Figure 2. Moreover, local RAS has a 101ort

role in the extrapulmonary manifestations of COVID-19 in propagating and complicating phases of the disease. The relationship between local RAS and COVID-19 has been suggested in the 102 ort he 102 re within the established clinical backgrounds (Figure 3). From the genetic point of view, ACE2, ANPEP, and HMGB1 are important in this phase. ACE2 and ANPEP may be good candidates for vaccine studies. The potential future treatment options 102 ort he initial phase include Mas receptor agonists, Angiotensin 1-7, soluble ACE2, interferon, and Ankaferd Hemostat. The association between COVID-19 infection, RAS, and hematopoiesis is very important, and topical soluble ACE2 has already been developed 102 ort he pharmacological management of COVID-19 infection based on future controlled clinical trials (89).

MAS receptor agonists and Angiotensin (1-7)

The MAS receptor is important in the Renin-Angiotensin-Aldosterone System (RAS). The ACE2 cleaves an amino acid from angiotensin I to form angiotensin (1-9) and cleaves an amino acid from angiotensin II to form angiotensin (1-7). The main action of the angiotensin (1-7) is the activation of the MAS receptor, inducing kinases that lead to the activation of endothelial nitric oxide synthase. The ACE2/Mas pathway regulates opposing physiology to ACE and angiotensin II. MAS receptor agonists have also shown organ protective effects in a number of animal studies. Currently, there are only limited pre-clinical studies (87). MAS receptor agonist may be a future treatment option since it blocks COVID-19 spread mechanisms at the initial phase of the disease. Moreover, local paracrine/ autocrine/ intracrine tissue-based RAS in the lung, bone marrow, and a wide variety of organs could participate in the genesis of COVID-19 immune syndrome (Figure 3).

The importance of induction of angiotensin-(1-7)/Mas receptor axis for correcting pathological conditions in COVID-19 through its anti-fibrotic, anti-inflammatory, vasodilatory, and cardioprotective effects is indicated by the failure of angiotensin II type 1 receptor blockers to control the severity of SARS-CoV-2 infections (87). TXA127 is a pharmaceutical formulation of the naturally occurring peptide, Angiotensin (1-7), and it has been developed for rare neuromuscular and connective tissue diseases (90). This drug may have the potential to be a future treatment option if drug re-positioning may be applied in COVID-19 patients who have neurological and hematological involvement.

Soluble ACE2

In a recent study, it has been demonstrated that SARS-CoV-2 can directly infect engineered human blood vessel organoids and human kidney organoids, which can be blocked by soluble ACE2. Those data demonstrated that soluble ACE2 could be effective, particularly in the early stages of SARS-CoV-2 infections (91). Recombinant Human Angiotensin Converting Enzyme 2 (rhACE2) is already being investigated for acute lung injury (92). Moreover, a drug named APN01, which is a rhACE2 is now under Phase-2 clinical trial 102 ort he treatment of COVID-19. APN01 deactivates the 102ort by binding to the viral particles with antibody-like affinity and avoids infection of target cells. Furthermore, APN01 has enzymatic activity that normalizes COVID-19-induced RAS deregulation. This drug may be used 102ort he future treatment of COVID-19 (93).

Interferon (IFN)

SARS-CoV-2 infection can result in the overproduction of many pro-inflammatory cytokines, but the production of type I interferon, which is the central anti-viral mediator, is blunted. The imbalanced interferon responses may contribute to the pathology of COVID-19 (94). IFN treatment has previously shown mixed efficiency against the SARS-CoV and MERS-CoV. Moreover, SARS-CoV-2 is probably more sensitive to interferon than the other coronaviruses. The IFNβ subtype seems to be the most appropriate for COVID-19 treatment. In a recent study, it is proposed that interferon treatment should be performed in the early stages of the infection (95). IFNs can be the potential future treatment options for COVID-19.

Ankaferd Hemostat (ABS)

High mobility group box-1 (HMGB1) molecule can lead to severe pulmonary inflammation in COVID-19 (96). The pathogenic impact of HMGB1 on SARS and disease management with herbal formulations targeting this unique protein has been proposed. Glycyrrhizin (a component of Ankaferd Hemostat) suppresses the HMGB1 (97). The ongoing outbreak of COVID-19, caused by the coronavirus SARS-CoV-2 last December, leads researchers to drug re-purposing (also called drug re-positioning, re-profiling, or re-tasking) strategies for identifying new uses of approved or investigational drugs that are outside the scope of the original medical indication. Ankaferd Hemostat (Ankaferd Blood Stopper®, ABS) is a traditional medicinal plant extract containing the extracts of a standardized mixture of five different plants. These are listed as follows: Thymus vulgaris (dried grass extract) (5.0 g/100 mL), Glycyrrhiza glabra (dried leaf extract) (7.0 g/100 mL), Vitis vinifera (dried leaf extract) (8.0 g/100 mL), Alpinia officinarum (dried leaf extract) (7.0 g/100 mL), and Urtica dioica (dried root extract) (6.0 g/100 mL) (98, 99). PubMed search shows that there have been published 235 papers to date investigating hemostatic properties, antimicrobial properties, regenerative and anti-apoptotic properties, anti-neoplastic and anti-apoptotic effects of ABS (https://pubmed.ncbi.nlm.nih.gov/?term=ankaferd&sort=date). Based on its previous clinical indications 102 ort he healing of cancer chemotherapy-induced oral/ gastrointestinal mucositis (98, 99), ABS may be beneficial in preventing oropharyngeal and pulmonary mucosal damage induced by COVID-19. ABS has antimicrobial, antiinfective, virucidal, antiseptic, and wound-healing features (97). The use of ABS prior to etoposide chemotherapy may increase

the response of melanoma cell lines because of the alteration of OXPHOS
genes (100). ABS inhibits the HMGB1 molecule, a pro-inflammatory cytokine, pathologically active in the processes of infection, inflammation, and cancer. The potential clinical usage of topical ABS and/or inhalation ABS preparation capable of targeting HMGB1 for the clinical management of COVID-19 has been suggested based on future clinical trials (101). ABS is an approved hemostatic agent 103 ort he treatment of dental, dermal, external, and internal bleeding (98, 99). Its non-toxic and non-irritable features make it possible to be applied as a topical oral solution. The current pharmaceutical dosage form of ABS is approved as a small-dosage topical formulation. We suggested that a small dosage topical formulation of ABS might be diluted as 1:10 v/v, 1:20 v/v, and 1:40 v/v with water and could be applied to the patients as a gargling solution. Re-purposing of the topical oral usage of ABS against COVID-19 may be clinically followed up, and further clinical investigations could be performed within the near future (97, 101).

BCG Vaccine

Some epidemiological studies have proposed a negative association between the national Bacillus Calmette–Guérin (BCG) vaccination policy and the prevalence and mortality of COVID-19. In a recent study, it has been shown that a strong correlation between the BCG index, an estimation of the degree of universal BCG vaccination in a country, and COVID-19 mortality in different socially similar countries was detected, representing that every 10% increase in the BCG index was related with a 10.4% decrease in COVID-19 mortality (102). The exact mechanism is not clarified since little is known about the capacity of BCG vaccination to confer broad immune enhancement and the functional correlates of protection. However, studies fail to confirm the null hypothesis of no relationship between BCG vaccination and COVID-19 mortality, and they propose that BCG could have a protective effect. On the other hand, many challenges are present for effective vaccine development against COVID-19 syndrome. In a recent study, it was stated that antibody-dependent enhancement (ADE) of disease is a general problem 103ort he development of vaccines. At present, no clinical data, immunologic assays, or biomarkers are known to differentiate any severe viral infection from immunity-related disease, whether by antibodies, T cells, or intrinsic host responses. Moreover, the other problem is that in vitro systems and animal models do not predict the risk of ADE disease, in part because protective and potentially detrimental antibody-mediated mechanisms have the same pattern (103).

TREATMENT STRATEGIES FOR COVID-19 PHASE II (PROPAGATING PHASE)

In this second phase of COVID-19, the disorder has already settled into the lungs and started to spread all over the body. The disease may have the potential to spread out cardiac, hematopoietic, nervous, ocular, renal, pancreatic, and other tissues of the numerous organ systems. EGFR and IGF2R genes have critical roles in this expanding phase of COVID-19 (7).

Epithelial response activates EGFR by generating signaling cascades, thereby having crucial and functional roles in the immune response against respiratory infectious diseases. Toll-like receptors (TLRs) are essential 103 ort he recognition of pathogens entering the body, and their interaction with EGFR is vital 103ort he development of the innate immune system (104, 105). In this way, EGFR down-regulation may be associated with the prevention of an early immune response, which can lead to the progression and spread of viral infection.

Another important gene in the propagating phase is IGF2R which encodes a receptor for 103ort he-like growth factor 2 and mannose 6-phosphate. It has been shown to be low expressed due to the viral infection. This receptor, which has different binding sites in different segments, has various functions, such as intracellular transport of lysosomal enzymes and conversion of growth factor-beta activation. As a result of low expression of IGF2R, normal IGF2R functions are impaired. This probably facilitates the virus's entry into the cell, and apoptosis occurs (106).

Current Treatment Strategies

In this phase of COVID-19, the disorder reaches into the lungs and starts to spread all over the body. Therefore, the current management approaches such as hydroxychloroquine/chloroquine, favipiravir, lopinavir-ritonavir, remdesivir, molnupiravir, dexamethasone, tocilizumab, and interferon beta could be mentioned herein as well.

Future Treatment Strategies

The EGFR and IGF2R genes regulate 103ort penetration and replication as well as an immune response against viral infection in this phase. Moreover, they are related to risk factors (hypertension and diabetes mellitus) for severe COVID-19. They can be used as a prognostic marker for severe COVID-19 patients. Any treatment agents targeting these genes may have the potential to inhibit SARS-CoV-2 to proceed to the third phase. Future studies are needed to confirm this hypothesis. Also, IFN genes have the potential for a treatment strategy in this phase. In a recent study, it was demonstrated that the treatment with IFN-α2b with or without arbidol significantly reduced the duration of detectable 103 ort in the upper respiratory tract and in parallel, reduced the duration of elevated blood levels 103ort he inflammatory markers IL-6 and CRP (93). Therefore, agents that target IFN can be used for COVID-19 patients who are in the second phase of the disease.

TREATMENT STRATEGIES FOR COVID-19 PHASE III (COMPLICATING PHASE)

In this final terminal phase, COVID-19 has the potential to spread all over the human body. Treatment options and treatment success are worse than in the previous phases. The genomic changes in the first two phases of COVID-19

lead to immunogenomic impairment in the third phase. In its severe form, the disease is characterized by ARDS, and there are no targeted intervention strategies to treat or prevent it. The immune response is thought to both have a role in the pathogenesis of disease and provide protection during its resolution. Thus, understanding the immune response to SARS-CoV-2 is of the utmost importance for developing and testing vaccines and therapeutics (107). The elevated circulating levels of cytokines associated with a variety of infectious and immune-mediated conditions are frequently termed a cytokine storm. There are protective functions of cytokines in optimal responses. However, if it is impaired by some multi-factorial origins, it can drive these responses to become pathological. It may lead to vascular damage, immunopathology, and worsening clinical outcomes (108). IFN and other immune genes are involved in various critical innate and adaptive immune responses in the third phase of COVID-19. IFN genes have a role in macrophage-associated syndrome and cytokine storm, which could be encountered in patients with COVID-19.

Cells generate an innate immune response via the cytokines, chemokines, and interferon-derived genes (ISGs) to the virus-infected cells and maintain this condition. As with many other viral infections, the amount and timing of IFNs are very important in COVID-19 (13, 109). Cytokines, chemokines, and ISGs, which have essential roles in the innate immune response against viruses, have been shown to be over-expressed in the complicating phase. The interferon type I (IFNI) signaling pathway contains two genetically and functionally distinct families of genes (IFIT (the IFN-induced protein with tetratricopeptide repeats) family and IFITM (the IFN-induced transmembrane protein) family) that inhibit various viral infections such as coronavirus. IFIT proteins induced after IFN show their anti-viral effects by inhibiting protein translation (110, 111). From these two crucial gene families, IFITM proteins are shown to be up-regulated in both SARS-CoV and SARS-CoV-2 and stop the replication of enveloped viruses before entering the cytosol.

Recent studies demonstrated that IFNs could play an important role in the effective treatment of COVID-19 (112). Generally produced in the process of viral or bacterial infections, IFN1 and IFN3 cause an increase in the expression of ordinarily low-expressed IFIT genes.

Current Treatment Strategies

Convalescent Immune Plasma

Convalescent plasma (CP) is acquired from individuals who have recovered from the infection and have generated an immune response against the infecting pathogen. Neutralizing antibodies are thought to be the main active component; other immune mediators of cellular origin may also contribute. Even though the 'mechanism of action' of the immune plasma is not fully delineated, CP therapy could result in an improvement in survival. CP treatment is of interest as no vaccine or specific treatment is available for COVID-19. In a recent study, authors proposed that in COVID-19 patients who do not need mechanical ventilation, CP therapy may be a curative treatment option (113). In another study, 103 patients with severe or life-threatening COVID-19 were randomly assigned to receive standard treatment with or without CP (114). Among the subset of patients who had severe but not life-threatening diseases, the rate of clinical improvement was more significant with immune plasma (115).

Future Treatment Strategies

GM-CSF

In a recent study, it was stated that GM-CSF administration in patients with COVID-19 could improve lung function by strengthening the alveolar wall and enhancing viral clearance (116). On the other hand, GM-CSF or GM-CSFR inhibition could be a beneficial treatment for the cytokine storm and inflammatory myeloid cell tissue infiltration related to moderate-to-severe COVID-19. GM-CSF inhibition strategies may have broad immunomodulatory roles, given that they could affect the production of multiple pro-inflammatory cytokines and chemokines by myeloid cells.

Interferon (IFN)

In a recent study, it was suggested that type-I IFN deficiency in the blood is related to severe COVID-19 and could identify the high-risk population. The authors have proposed testing of IFN administration combined with adapted anti-inflammatory therapy targeting IL-6 or TNF-α in most severe patients (117). Future studies are needed to investigate agents that interfere with IFN and other immune genes in the third phase of the disease.

CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, there is no single effective treatment for COVID-19 in all clinical settings to date, and the disease has turned into a global disaster. We suggest that understanding the disease's unique phases and underlying genomic features are the keys to reaching an effective solution for COVID-19. In this review, we have proposed several potential treatment agents for the management of COVID-19 (Table 1). ACE and ANPEP, EGFR and IGF2R, IFN, and other immune genes are the critical genes for the initiating, propagating, and complicating phases of COVID-19, respectively. In this review, we propose that MAS receptor agonists, angiotensin (1-7), TXA127, soluble ACE2, APN01, interferons, ABS, BCG vaccine, and GM-CSF agonist/inhibitors have the potential for the future treatment of COVID-19 because of their clinicobiological features. Further clinical and experimental studies should be performed in order to effectively fight against the currently ongoing global disaster of COVID-19.

Table 1. Potential treatment agents for the management of COVID-19 that shall be tested in future clinical trials

DRUG	CLINICAL EXPERIENCE	BIOLOGICAL BASIS	FUTURE PERSPECTIVE
Mas receptor agonists	Candidate drugs of this pathway have not been investigated in clinical studies	The ACE2/MAS pathway regulates opposing physiology to ACE and angiotensin II	Mas pathway agonists might potentially block the COVID-19 spread mechanisms at the initial phase of the disease
Angiotensin (1-7)	Ang (1-7) drug has been developed for rare neuromuscular and connective tissue diseases	Ang (1-7) drug has the potential to correct pathological conditions of COVID-19 through its anti-fibrotic, anti-inflammatory, vasodilatory, and cardioprotective effects	Ang (1-7) may have potential if drug re-positioning could be applied to COVID-19 patients who have neurological and/or hematological involvements
Soluble ACE2	Recombinant Human Angiotensin Converting Enzyme 2 (rhACE2) is being investigated for acute lung injury	SARS-CoV-2 can directly infect engineered human blood vessel organoids and human kidney organoids, which can be blocked by soluble ACE2. The drug has enzymatic activity that normalizes the COVID-19-induced RAS deregulation	Topical soluble ACE2 can be effective, especially in the early stages of SARS-CoV-2 infections
Interferon (IFN)	Currently, IFN preparations are being used as biological response modifiers in a wide variety of clinical settings	SARS-CoV-2 can result in the overproduction of pro-inflammatory cytokines, but the production of type I interferon is blunted. IFN treatment has shown mixed efficiency against SARS-CoV and MERS-CoV	The IFNβ subtype seems to be the most appropriate for COVID-19 treatment
Ankaferd Hemostat (ABS)	ABS is an approved hemostatic agent for the treatment of dental, dermal, external, and internal bleeding	Glycyrrhizin (a component of ABS) suppresses the HMGB1. HMGB1 can lead to severe pulmonary inflammation in COVID-19.	The potential clinical usage of topical ABS and/or inhalation ABS preparation capable of targeting HMGB1 for the oropharyngeal and pulmonary mucosal damage of COVID-19 has been suggested based on future clinical trials
BCG Vaccine	Vaccine (historical)	The exact mechanism is not clarified since little is known about the capacity of BCG vaccination to confer broad immune enhancement and the functional correlates of protection	Studies fail to confirm the null hypothesis of no relationship between BCG vaccination and COVID-19 mortality and propose that BCG could have a protective effect
GM-CSF	Already approved drug for the treatment of leucopenia/ neutropenia	Improve lung function by strengthening the alveolar wall and enhancing viral clearance. Inhibition could be a beneficial treatment for the cytokine storm and inflammatory myeloid cell tissue infiltration of COVID-19	The drug may have immunomodulatory roles, given that it could affect the production of multiple pro-inflammatory cytokines and chemokines by myeloid cells

(ACE: angiotensin converting enzyme, Ang: Angiotensin, BCG: Bacille Calmette-Guérin, COVID-19: Coronavirus Disease 2019, GM-CSF: Granulocyte-macrophage colony-stimulating factor, HMGB1: High mobility group box 1)

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