

# Prospective approach to manage COVID-19-related cytokine storm; an updated review on current concepts



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## Abstract

Coronavirus disease 2019 or COVID-19, caused by the novel human coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in late 2019, in the city of Wuhan, Hubei province, China. Unfortunately, despite many efforts to find cures for SARS-CoV-2 disease, still the management of severe cases remains challenging. In severe forms of COVID-19, proinflammatory cytokines are notably elevated (3) and reminiscent of the secondary hemophagocytic lymphohistiocytosis (HLH). According to many studies, immune imbalance and an uncontrolled massive release of inflammatory cytokines have a significant role in COVID-19 severity and ARDS pathophysiology. Accordingly, targeting the over-activated immune system to prevent tissue damage is now one of the most noticed possible strategies to manage severe COVID-19 cases. In the present study, we reviewed studies and clinical trials conducted in this regard.

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## Introduction

Coronavirus disease 2019 or COVID-19, caused by the novel human coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in late 2019, in the city of Wuhan, Hubei province, China. The virus was rapidly transmitted from human to human with a global spread, and it was further declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 (1). Up to December 18, 2020, there were 72 851 747 confirmed cases and 1 643 339 related deaths (2).

Coronaviruses have existed for a long time and have often been identified as the causes of mild gastrointestinal or respiratory illnesses. However, coronaviruses with high pathogenicity causing severe diseases have emerged over the past two decades; severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), which appeared in Guangdong province of China in 2002, and Middle East respiratory syndrome coronavirus (MERS-CoV), which caused a breakout in the Middle East in 2013. Both these diseases and COVID-19 had animal origins (zoonotic diseases) (1). Most of the time, COVID-19 appears initially with fatigue, fever, loss of appetite, cough,

## Key point

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diarrhea, and myalgia. Various complaints like shortness of breath and subsequent acute respiratory distress syndrome (ARDS) were detected in severe cases. In these cases, kidney, liver, and heart damage can also eventually induce shock and death (3). This virus transmitted via respiratory aerosols of an infected individual, after inhalation by other persons, infects them (4).

Coronaviruses belong to the Coronaviridae family, Nidovirales order. They are the enveloped viruses with a positive-sense single-stranded RNA genome. They are also intersected into four genera: alpha, beta, gamma, and delta, according to the electron microscopic findings. The novel coronavirus belongs to the beta-coronaviruses genus. These viruses have projections on their envelope surfaces called “spike glycoprotein,” or S protein (5). The virus enters the cells by the interplay between ACE-2 on the host cellular surface and viral spike protein (6). This receptor presenting on the surfaces of

different human cells such as proximal tubular kidney cells, lung epithelial cells, cardiovascular tissue cells, and gastrointestinal tract, causes the infection of these cells by the virus and subsequent related manifestations (7). Unfortunately, despite many efforts to find cures for SARS-CoV-2 disease. Therefore, the management of severe cases remains challenging (8). In October 2020, the US Food and Drug Administration (FDA) approved remdesivir to treat hospitalized patients with SARS-CoV-2 of 12 years of age and older and a weight of at least 40 kg. Its rationale was several phase 3 clinical trials on hospitalized individuals with various disease severities (9). It is the only drug with FDA approval for this virus. Other remedies only have received Emergency Use Authorization (EUA) (10).

“Cytokine storm,” first used to describe graft-versus-host disease in 1993, is an overreaction of the host immune system to an infectious agent that causes severe tissue damage and death. While the inflammatory cytokines help fight the pathogen, the exact line between the appropriate immune response and the over-harmful response is unclear, and a sole definition for this term has not yet been admitted. In general, immune system disorders, leading to multi-organ failures, called the cytokine storm. This cytokine storm creates fatigue, fever, neurological symptoms, myalgia, diarrhea, anorexia, and rash. It may also lead to disseminated intravascular coagulation, cholestasis, kidney damage, cardiovascular injury, and ARDS (11). Manifestations of this syndrome are mainly due to the inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$ , IL-1, IL-6, and IL-18, while both inflammatory and anti-inflammatory mediators elevate in the cytokine storm. Cytokine storm was previously reported in SARS-CoV and MERS-CoV (12,13), influenza H1N1 (14), and influenza H5N1 (15) (16)

In severe forms of COVID-19, pro-inflammatory cytokines are notably elevated (3) and reminiscent of the secondary hemophagocytic lymphohistiocytosis (HLH) (17). It is assumed to be involved in the development of several serious and potentially fatal disease complications such as thromboembolic events, ARDS, vasculitis, encephalitis, acute renal and liver damages, and neurological involvement and also may be a key in the development of a more severe illness in the elderly and individuals with comorbidities (7,18). According to many studies, immune imbalance and an uncontrolled massive release of inflammatory cytokines have a significant role in COVID-19 severity and ARDS pathophysiology (19). Accordingly, targeting the over-activated immune system to prevent tissue damage is now one of the most noticed possible strategies to manage severe COVID-19 cases.

In the present study, we reviewed studies and clinical trials conducted in this regard.

## Methods

Data were collected in Scopus, EBSCO, Google Scholar, Web of Science, and PubMed databases. The

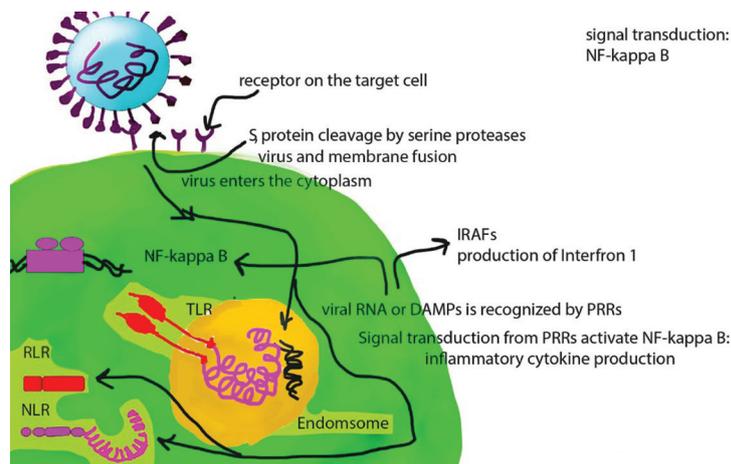
keywords used SARS-CoV-2, COVID-19, inflammation, pathogenesis, immunotherapy, anti-inflammatory, immunomodulation, coronavirus, cytokine storm, and cytokine release syndrome. In addition to search terms, we limit data collection to research and review articles written in English only.

## Current knowledge about SARS-CoV-2 pathogenesis

This virus binds to ACE2 on the target cell by its S protein and after that, S protein cleavage by a protease like cathepsin facilitates virus and membrane fusion and virus entry to the target cell (8). Following the extensive cellular damage after becoming infected with the virus, dead cell debris can elicit a macrophage-dependent inflammatory response (20). Endothelial cells are also contributed to the pulmonary damage process as they facilitate the cumulating and extravasation of neutrophils and leukocytes (21). Accordingly, macrophages of the alveolar tissue express ACE2 and can become directly infected by the virus (20,22) (Figure 1). In severe forms of the disease, several abnormalities in the immune system function, including lymphopenia, neutrophilia, lymphocyte dysfunction, increased pro-inflammatory cytokines, monocyte, and granulocyte dysfunction, are seen. The proportion of neutrophils to lymphocytes is an essential predicting factor for disease severity. T-cells show elevated levels of T cell immunoglobulin domain and mucin domain-3 (TIM3), killer cell lectin-like receptor subfamily C member 1 (NKG2A), and programmed cell death protein-1 (PD1) on their surface (23). Interleukin-6 (IL6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interferon-gamma (IFN- $\gamma$ ), and interleukin-1 gamma (IL-1 $\gamma$ ) are released during the cytokine release phase (24), and severe cases are associated with a significant release of inflammatory mediators such as CRP, interleukin-6, and ferritin (25). Interstitial edema observed in SARS-CoV-2 victims' lung biopsies is mainly caused by incremented capillary permeability due to the effects of TNF (24). Besides, IP10, MCP1, IL-1RA, IL-1 $\beta$ , IL-2R, IL-6-10, IFN- $\gamma$ , TNF- $\alpha$ , GM-CSF, and G-CSF levels are heightened in both severe and non-severe SARS-CoV-2 infected individuals. However, it is more drastic in severe cases. GM-CSF produced by Th1 cells progresses the inflammatory process by inducing CD14+CD16+ monocytes and release of IL-6 (23).

Th-17 plays several pro-inflammatory roles by producing GM-CSF, IL-17, IL-21, and IL-22. However, the immune system must fight against pathogens. TNF- $\alpha$  and IL-1 $\beta$  raise its function. The presence of the Th-17 linked cytokine storm has been observed in COVID-19, H1N1 influenza, MERS-CoV, and SARS-CoV (26).

In one post-mortem investigation, two victims' lung biopsies showed filling of the alveoli with lymphocytes, neutrophils, macrophages, and diffuse alveolar damage. Alveolar macrophages in these patients had expressed significant levels of programmed death-ligand 1, IL-10, IL-6, and TNF- $\alpha$ . Alveolar macrophages are key immune



**Figure 1.** After a pathogen enters the human's body, it is recognized by PRRs in the innate immune system, and when target cells get infected with the pathogen, damage-associated molecular patterns (DAMPs) are recognized by them. The production of inflammatory cytokines enhances through signaling from these receptors. The genes of these cytokines are expressed following the activation of the NF kappa B pathway. Following activation of the IRF pathway, after TLRs or RLRs recognize the viral RNA, the antiviral response is induced by interferons' expression. Additionally, macrophages can get directly infected by SARS-CoV-2 as they express ACE 2; NF-kappa B. S protein (spike protein), TLR (toll like receptor), NLR, NOD like receptor, RLR, PRR and IRAF.

cells in the development of cytokine release syndrome in the course of SARS-CoV-2 (6). Although inflammatory mediators are increased in SARS-CoV-2 patients, the IFN-1 ( $\alpha$ ,  $\beta$ ) related response is attenuated and delayed (27), which is vital in the host defense against viruses. However, some other studies have shown that IFNs are increased in severe forms of the disease and may be associated with disease severity (28).

Hyper-inflammation and immune response failure (immunoparalysis) are present in this disease; the proportion of these two differs in different individuals and different disease stages. Although IL-10 is an anti-inflammatory mediator, it was significantly related to the disease intensity and acute renal failure development in COVID-19 patients in a previous study, even more than pro-inflammatory mediators such as IL-6. This virus can infect lymphocytes and then, IL-10 production results in cell apoptosis and causes lymphopenia (29). According to the immune response against the virus, there are three phases in SARS-CoV-2 disease. In the first phase, PAMPs (pathogen-associated molecular pattern) activates the innate immune system. In the second phase, the adaptive immune system acts, and the patient becomes symptomatic. In the third phase or the cytokine release phase, severe symptoms appear due to the excessive release of inflammatory mediators (30). In general, an imbalanced immune response leads to cytokine storm development and organ failure (21,30-33) (Figure 2).

### Potential therapeutic options to manage SARS-CoV-2 related cytokine storm

#### Corticosteroids

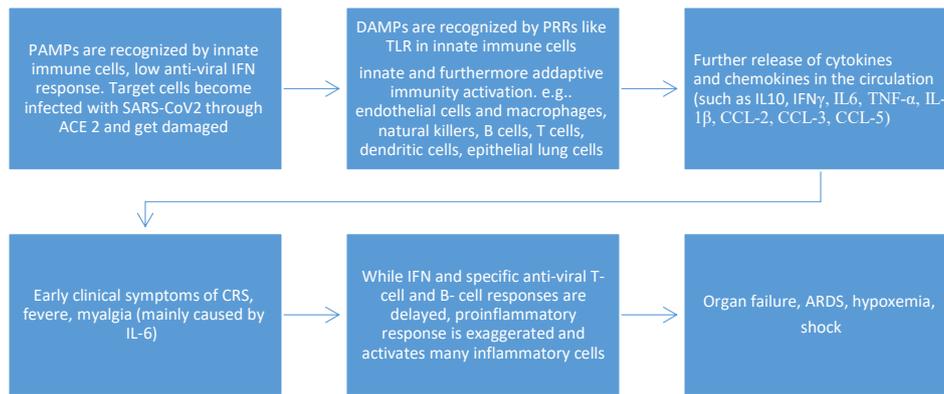
In previous studies, early administration of corticosteroids in MP infections and influenza has been influential in the recovery of pulmonary lesions (33). In a meta-analysis of seven clinical trials (including 1703 seriously ill SARS-

CoV-2 patients), three trials were on dexamethasone, one on methylprednisolone, and three on hydrocortisone. In this study, corticosteroid therapy was associated with a decreased all-cause mortality rate 28 days after randomization with no serious safety concerns. However, severe adverse effects were reported in six trials (18.1% of the individuals randomized to the corticosteroids treated group) (34). In a retrospective study in Wuhan during the first months of the disease on 102 seriously ill SARS-CoV-2 patients, 69 patients received methylprednisolone, and others did not receive it. Regarding disease prognosis and clinical improvement, no significant difference was found comparing these two groups (35). In adult patients with SARS-CoV-2 and ARDS, systemic use of corticosteroids is suggested because it is shown to reduce mortality in these cases (17).

Corticosteroids have been previously used to treat SARS-CoV and MERS-CoV pulmonary diseases, but they did not show enough efficacy and even were damaging (36). A meta-analysis of 15 cohort studies on the effects of corticosteroids in patients with influenza showed that these drugs were associated with heightened mortality rates (17). Recently, a preliminary report of a multi-center randomized open-labeled clinical trial (RECOVERY) indicated the positive effects of dexamethasone in clinical improvement of severely ill SARS-CoV-2 patients who needed supportive respiratory care but not in patients who did not need supplementary oxygen (37).

#### Anti-IL-6

As IL-6 plays a crucial role in the cytokine storm, agents that reduce IL-6 signal transduction may barricade from fatal SARS-CoV-2 complications (38). To this rationale, attention has been recently paid toward IL-6 blockade to manage COVID-19 severe cases. Tocilizumab, siltuximab, and sarilumab are medications with anti-IL-6 activities



**Figure 2.** Cytokine storm development in the course of COVID-19.

(39). Tocilizumab was first constructed in the 1990s and is one of the first drugs used to suppress the immune system. It is a monoclonal antibody against the human IL-6 receptor (11). Many studies have assessed the effectiveness of this drug in the treatment of COVID-19 and found different results. According to the results of a meta-analysis study, tocilizumab could reduce the mortality rate in severe COVID-19 patients (40). Results of clinical trials are also repugnant (25,41,42).

#### **Anti-TNF**

According to a meta-analysis, these agents improve patients' survival in sepsis (43). TNF causes pulmonary capillary leakage in patients with COVID-19 (44). Biological agents that antagonize the inflammatory cascade of TNF may have beneficial effects in the treatment of SARS-CoV-2. Accordingly, inflammatory bowel disease patients under anti-TNF therapy had lower mortality rates than those under sulfasalazine, mesalamine, or steroid therapies. The risk of super-infection may increase with the use of these antibodies (45). Additionally, these medications have been entered in randomized clinical trials (#NCT04425538).

#### **Interferon**

Although IFN 1 is essential in the defense against viruses, it also has pro-inflammatory activities, shown in mouse models of SARS (46).

Nebulized interferon alfa-2b in addition to umifenovir decreased systemic inflammation compared with umifenovir alone in a retrospective cohort study. In this study, there were 77 participants, and patients in the treatment group were significantly younger than those in the control group (47). Interferon  $\alpha$  and  $\beta$  are currently under investigation in clinical trials.

#### **Janus kinase (JAK)/signal transducers and activators of transcription (STAT) inhibitors**

Although JAK/STAT signaling is crucial in viral eliminating and IFN response, it plays a significant role in activating the immune cells and developing the cytokine storm. Viruses

like the novel coronavirus can escape from the immune system by inhibiting this pathway. JAK/STAT signaling is activated after inflammatory mediators such as IL-6 or IFN bind to their target cells' receptors. Ruxolitinib, a JAK 1 and 2 inhibitor, is currently being evaluated under a phase 3 clinical trial for its efficacy in reducing SARS-CoV-2 serious complications in hospitalized individuals (48). Fedratinib, a JAK2 inhibitor, reduces IL-17 production by Th-17 cells and eventually prevents Th-17 related cytokine storm in mice models (26). JAK inhibitors can inhibit the phosphorylation of proteins being necessary for signal transduction by cytokines (49).

#### **Anti-IL-23 and 17**

Recent studies showed that IL-23 and IL-17 blockade had been accompanied by positive effects in COVID-19 in psoriasis patients (50). Ixekizumab is an IL-17A binding monoclonal antibody. This drug's effect after adding to the antiviral therapy is currently under investigation in a clinical trial (50). There is not further clinical data available on the effect of these drugs in COVID-19.

#### **Antimalarial medications**

Hydroxychloroquine is an antimalarial drug with anti-inflammatory effects used in the treatment of SLE and RA. This drug was previously recommended in SARS-CoV-2. However, scientists advised that its use should be with caution due to the possible adverse effects (51). Currently, chloroquine or hydroxychloroquine are not recommended in either non-hospitalized or hospitalized individuals with SARS-CoV-2 for treatment (52).

Another antimalarial drug is artesunate. A study in 2016 to evaluate the possible effects of artemisinin in managing burn-related sepsis in BALB/c mice found that neutrophil infiltration in the heart and lungs and inflammatory cytokines production was reduced in treated mice after randomization by preventing the NLRP3 inflammasome in macrophages. It lowered IL-18 and IL-1 $\beta$  levels in treated mice (53). In severe malaria cases, the production of inflammatory cytokines,

mainly TNF and IL-6, is heightened and correlates with the disease severity. After treatment with artesunate, the concentration of these inflammatory mediators reduced. (54) Immunomodulatory actions of artesunate are mainly through inhibiting NF $\kappa$ B (55). Moreover, in vitro artemisinin-based combination therapy activity against SARS-CoV-2 replication is shown in a study (56). Artesunate has recently entered COVID-19 clinical trials too.

#### **Anti-IL-1**

In a recent prospective cohort study, 78 seriously ill SARS-CoV-2 patients were evaluated for their clinical response to anakinra, an IL-1 receptor antagonist. In this study, the decrease in plasma concentrations of procalcitonin, ferritin, and white blood cell counts showed that this treatment effectively reduced the clinical inflammatory indicators (57). Another cohort study also reported that anakinra decreased death risk in the treatment group relative to the control group (58).

#### **Retinoic acid**

One recent study showed that retinoic acid was efficient in ameliorating human bronchial epithelial cell culture model (16HBE) function and attenuating the barrier leakage induced by inflammatory cytokines. This agent also affected the tight junctional complex and somewhat inversed TNF- $\alpha$ 's effects on these proteins (59).

#### **Mesenchymal stem cells**

A case report of successful SARS-CoV-2 treatment with human umbilical cord mesenchymal stem cells (hUCMSC) in a critically ill 65-year-old female patient with multi-organ failure showed that it was influential in clinical improvement. This patient had typical signs of COVID-19, a past medical history of diabetes and hypertension, and a positive RT-PCR test for this virus. A non-invasive mechanical ventilator was used, and the patient received Xuebijing, methylprednisolone, moxifloxacin, lopinavir/ritonavir, IFN-inhalation, and immunoglobulin for treatment. The patient developed multi-organ damage and ARDS despite the appropriate treatment, and she was transferred to the ICU. The patient also had elevated CRP, procalcitonin, and D-dimer levels in addition to relative lymphopenia and neutrophilia. After administration of the allogeneic hUCMSCs in addition to thymosin  $\alpha$ 1, the patient's clinical status improved, laboratory markers of organ injury went down, the lymphocyte count also was increased, and it was not associated with any serious adverse side effects. While thymosin  $\alpha$ 1 had been started for the patient before administering hUCMSCs, clinical improvement was probably the result of hUCMSCs administration (60).

Furthermore, in a randomized clinical trial on 41 SARS-CoV-2 patients, 12 patients who received hUCMSC showed less mortality and clinical deterioration than the

control group; however, this difference was not significant. In the treatment group, inflammatory mediators like IL-6 went down faster, and diabetic patients in this group had a lessened need for insulin. The efficacy, safety, and exact mechanism through which hUCMSC could help treat the severe SARS-CoV-2 cases need further investigation. However, there is evidence showing its immunomodulatory effects and ability for tissue repair (61).

#### **Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) has immunomodulatory effects with unknown mechanisms. In treating COVID-19 encephalopathy, it has been effective and safe in clinical improvement and decreasing inflammatory mediators (62). It is used in the treatment of viral and bacterial sepsis. A cohort study showed that IVIG could significantly decrease mortality and the inflammatory response and ameliorated organ failure in patients with critical status. In this study, an initial high-dose administration of IVIG (>15 g/d) was effective in seriously ill patients and improved prognosis (63).

#### **Antibiotics**

Doxycycline has anti-inflammatory effects and has been effective in SARS-CoV-2 patients' clinical improvement in recent clinical trials. However, due to the risk of microbial resistance, its use should be with caution and restricted, and it is not recommended in mild to moderate cases (64).

#### **Metformin**

Metformin is a biguanide used to treat diabetes mellitus that has mitochondrial effects. Mitochondria has a role in programmed cell death related to the release of apoptotic signaling molecules (65). Metformin can inhibit NF- $\kappa$ B signaling and mitochondrial enzymes and, therefore, gene expression of inflammatory cytokines like IL-6 (66). A meta-analysis of five studies with 6937 patients showed that metformin decreases COVID-19 related mortality rates (67).

#### **Convalescent plasma**

The convalescent plasma from recovered individuals with sufficient antibody titers has been attracted attention as a therapeutic option (68). There are many ongoing clinical trials in this regard; for example, RESCUE is an ongoing clinical trial to evaluate convalescent plasma's efficacy and safety in treating old-aged adults with SARS-CoV-2.

#### **Other agents with possible anti-inflammatory effects**

Icosapent ethyl is a remedy to control hypertriglyceridemia if the maximum dosage of statins is insufficient. This drug has anti-inflammatory functions, and a recently published study revealed its efficacy in the clinical improvement of three COVID-19 patients admitted in ICU (69).

Several pharmaceutical active natural products (PANPs) have shown anti-inflammatory effects and lung protection against ARDS in animal models. For example, in previous

studies, omentin and vaspin mitigated inflammatory response in mice with ARDS induced by lipopolysaccharide (LPS), berberine inhibited NF- $\kappa$ B pathway activation, and tetrahydroberberine was associated with a decrease in inflammatory mediators' levels like TNF $\alpha$  (21).

Emodin is a plant-extracted flavonoid. In mouse models of asthma, it has shown anti-inflammatory effects by preventing STAT6 (signal transduction and activation of transcription) phosphorylation and activated macrophage polarization. Another flavonoid, scutellarein, inhibits the NF- $\kappa$ B pathway and subsequently suppresses the expression of inducible nitric oxide synthase and cyclooxygenase-2 (8).

A study on severe SARS-CoV-2 patients' peripheral blood mononuclear cells indicated that GSK-LSD-1, an inhibitor of lysine-specific demethylase 1 (LSD1) phosphorylation, reduced cytokine production in vitro. Phosphorylated LSD1 stabilizes NF- $\kappa$ B p65 to regulate the gene expression of pro-inflammatory cytokines (70).

Peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) is a nuclear receptor that has a role in inflammation through regulating related gene expression and is vastly expressed in the adipose tissue. Gamma-oryzanol has shown a reduction in adipose tissue inflammatory status in male Wistar rats treated with this agent in a previous study (71).

Pentoxifylline, a xanthine derived drug, down-regulates the pro-inflammatory adenosine receptor A2A pathway (A2AR) and lowers expression rates of IL1b, IL6, TNF  $\alpha$ , ICAM1, IFN  $\gamma$ , VCAM1, and the production of inosine and adenosine. This drug diminishes cytokine release from the lung macrophages isolated from individuals with sarcoidosis. In rats, it ameliorates pulmonary function and glomerular injury, while in sepsis, down-regulates several inflammatory cytokines. Pentoxifylline does not have any direct antiviral effect (24).

### Ongoing clinical trials

Since the pandemic onset in December 2019, many clinical trials have been registered to evaluate the possible immunomodulation effects in COVID-19 prognosis. We provided a list of ongoing clinical trials concerning the main immunomodulatory treatments and their possible side effects in online Table S1.

### Conclusion

COVID-19 is currently a pandemic that has affected most countries around the world and millions of people. The possibility of its fatality in severe cases and the lack of any definitive vaccines or treatments necessitates the need for ongoing studies to find a cure. Targeting the cytokine storm with immunomodulatory medications is one of the potential treatment options, encouraging preliminary reports in some aspects. Performing further studies to evaluate the efficacy and safety of these remedies in the future is needed.

### Authors' contribution

Primary draft by MB. Edit of the manuscript by LS. All authors read and signed the final paper.

### Conflict of interests

The authors declare no conflict of interest.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Written consent was obtained from the patient for publication of the study.

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None.

### Supplementary Materials

Supplementary file 1 contains Table S1.

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