**Review Article**

# Weathering the Cytokine Storm in COVID-19: Therapeutic Implications

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**Abstract**

***Background:*** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recently emerged in Wuhan, Hubei-China, as responsible for the coronavirus disease 2019 (COVID-19) and then spread rapidly worldwide. While most individuals remain asymptomatic or develop only mild symptoms, approximately 5% develop severe forms of COVID-19 characterized by acute respiratory distress syndrome (ARDS) and multiple-organ failure (MOF) that usually require intensive-care support and often yield a poor prognosis. ***Summary:*** The pathophysiology of COVID-19 is far from being completely understood, and the lack of effective treatments leads to a sense of urgency to develop new therapeutic strategies based on pathophysiological assumptions. The exaggerated cytokine release in response to viral infection, a condition known as cytokine release syndrome (CRS) or cytokine storm, is emerging as the mechanism leading to ARDS and MOF in COVID-19, thus endorsing the hypothesis that properly timed

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anti-inflammatory therapeutic strategies could improve patients' clinical outcomes and prognosis. ***Key Messages:*** The objective of this article is to explore and comment on the potential role of the promising immunomodulatory therapies using pharmacological and nonpharmacological approaches to overcome the dysregulated proinflammatory response in COVID-19.

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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recently emerged in Wuhan, Hubei-China, as responsible for the coronavirus disease 2019 (COVID-19) and then spread rapidly worldwide. It was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1, 2].

While most individuals remain asymptomatic or develop only mild symptoms, up to 15–20% require hospitalization and less than 5% develop a critical illness characterized by acute respiratory distress syndrome (ARDS) and multiple-organ failure (MOF) that usually need intensive-care support and often yield a poor prognosis [3]. In most cases, patients presenting to the emergency room have not undergone prehospital ambulatory testing or, as a consequence, any ongoing treatment intended to reduce the severity of disease [4, 5]. The pathophysiology of COVID-19 is far from being completely understood, and the lack of effective treatments has led to a sense of urgency to develop new therapeutic strategies based on pathophysiological assumptions. The SARS-CoV2 spike protein initiates cellular infection by binding angiotensin-converting enzyme (ACE)-2 on human cells [6]. Cellular infection and viral replication cause activation of the inflammasome in the host cell, leading to the release of proinflammatory cytokines and cell death by pyroptosis with ensuing release of a damage-associated molecular pattern, further amplifying the inflammatory response [7–9]. The exaggerated cytokine release in response to viral infection, a condition known as cytokine release syndrome (CRS) (Fig. 1) or cytokine storm, is emerging as one of the mechanisms leading to ARDS and MOF in COVID-19 [7]. In line with this, recent studies have shown that patients with COVID-19 have high levels of inflammatory cytokines, such as interleukin (IL)-1$\beta$, IL-2, IL-6 IL-7, IL-8, IL-9, IL-10, IL-18, tumor necrosis factor (TNF)-$\alpha$, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, fibroblast growth factor, macrophage inflammatory protein 1, compared to healthy individuals [10]; circulating levels of IL-6, IL-10, and TNF-$\alpha$ also correlated with illness severity as they were significantly higher in intensive care unit (ICU) patients compared to mild/moderate cases. In particular, IL-6 may suppress normal T-cell activation [11], and TNF-$\alpha$ can promote T-cell apoptosis via interacting with its receptor TNF receptor 1 [12], and their upregulation may in part contribute to lymphocytopenia, a feature often encountered in COVID-19, with a more pronounced decline in severe cases [13]. As such, a recent study found that, in ICU patients due to COVID-19, TNF-$\alpha$ and IL-6 concentrations negatively correlated with total T-cell, CD4+, and CD8+ counts [14]. Furthermore, ACE-2 consumption by viral entry interrupts angiotensin II (AngII) metabolism, resulting in an initial increase in local AngII concentrations that may enhance proinflammatory cytokine release and foster diffuse microvascular dysfunction and a prothrombotic milieu [15, 16].

Antiviral treatment may play a role in the management of COVID-19 but, especially in more severe forms, immunomodulatory treatments blunting cytokine release may turn out to be beneficial if appropriately timed.

The objective of this article is to explore and comment on the potential role of the promising immunomodulatory therapies using pharmacological and nonpharmacological approaches to overcome the dysregulated proinflammatory response in COVID-19 (Fig. 1).
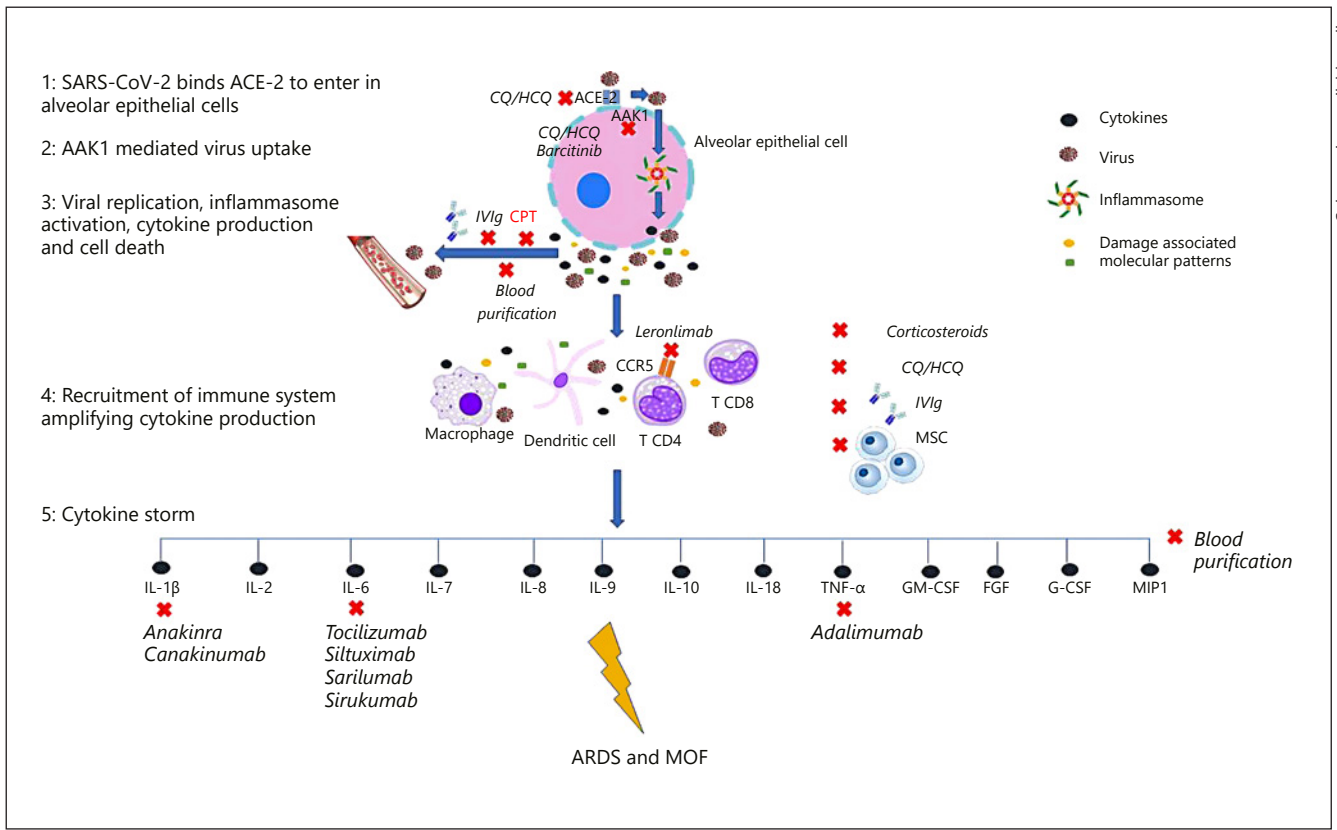
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**Fig. 1.** Cytokine storm consequent to SARS-CoV2 infection is emerging as the main mechanism leading to ARDS and MOF in COVID-19. Identification of patients with a hyperinflammatory response through cytokine profiling could direct the choice of a specific anticytokine drug or even combined/sequential regimens; in selected cases, implementation of broad-spectrum anti-inflammatory therapies, such as IVIg and blood purification, could be considered. AAK1, adaptor-associated protein kinase 1; CCR5, C-C chemokine receptor type 5; T CD, T-cell cluster of differentiation; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; MIP1, macrophage inflammatory protein 1.

## Corticosteroids

Despite being extensively used empirically in the treatment of severe forms of ARDS, the role of systemic corticosteroids (CS) remains controversial [17]. CS are the cornerstone of treatments for cytokine storms and macrophage activation syndrome in autoimmune/auto-inflammatory diseases [18]; in the COVID-19 scenario they may be useful in the more severe forms of CRS to curb the systemic inflammatory response and prevent the occurrence of ARDS, if appropriately timed [10, 19], 20]. On the other hand, the early use of CS seems to be outweighed by their adverse effects, such as impaired virus clearance and an increased rate of secondary bacterial or fungal infections [21]. In fact, a recent systematic review and meta-analysis in adult patients with influenza pneumonia demonstrated that CS increase not only mortality but also the rate of secondary infections and prolong the ICU length of stay [22]. For these reasons, the WHO does not recommend routine administration of CS in COVID-19 patients outside of clinical trials; their adjunctive use may be indicated on an individual basis or unless indicated for other conditions, such as chronic obstructive pulmonary disease, asthma, and septic shock [23].

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## Chloroquine and Hydroxychloroquine

The antimalaria drugs chloroquine (CQ) and hydroxychloroquine (HCQ) have been proven to interfere with the viral entry process through alteration of pH-dependent endosome-mediated viral endocytosis and could inhibit SARS-CoV entry through change of the glycosylation of the ACE2 receptor and spike protein. HCQ is less toxic than CQ and can be used for long periods of time [24]. Moreover, both CQ and HCQ have been proven to have immunomodulatory activities by interfering with Toll-like receptor signaling pathways, reducing cytokine production, and inhibiting MHC class II expression, antigen presentation, and immune activation through the reduction of CD154 expression in T cells [25–27]. The ability of CQ/HCQ to inhibit certain coronaviruses, such as SARS-CoV-1, has led to inclusion of the use of CQ/HCQ for the treatment of COVID-19. High-quality studies are, however, urgently needed to provide information on its effectiveness, address the optimal dose and duration of treatment, and explore its side effects and long-term outcomes. Since the earliest phases of the pandemic, CQ and HCQ have been empirically used alone or in combination with macrolides for the treatment of COVID-19 with the intent of reducing hospitalizations and deaths. Although several multicenter randomized controlled trials are underway, a recently published large observational multinational registry showed a decreased in-hospital survival and an increased frequency of ventricular arrhythmias in patients with COVID-19 requiring hospitalization treated with CQ/HCQ alone or in combination with a macrolide. However, these data do not apply to the use of CQ/HCQ in the ambulatory and outpatient settings and, due to the observational study design, the possibility of unmeasured confounding biases cannot be excluded. On the basis of this study, at present the use of CQ and HCQ is not recommended in hospitalized patients other than in the context of randomized trials.

## Cytokine-Targeting Therapies

IL-1β, IL-6, and TNF-α levels are upregulated in patients with COVID-19, especially in severe forms, and may play a central role in determining diffuse tissue damage associated with CRS [28], thus leading to the assumption that drugs inhibiting these molecules could be beneficial in reducing this exaggerated inflammatory response.

### IL-1 Blockade

Anakinra, an IL-1 receptor antagonist that blocks the biologic activity of IL-1, is a promising agent in this setting since it has already been shown to be effective in severe sepsis complicated by CRS macrophage activation syndrome [29, 30]. Recently Monteagudo et al. [31] reported 5 cases of a cytokine storm (2 with an identified viral trigger) in which continuous intravenous anakinra infusion resulted in prompt improvement in laboratory and clinical parameters. There are limited data with specific IL-1 blockers in patients with COVID-19. Cavalli et al. [32] reported on 29 patients with COVID-19 and ARDS managed with noninvasive ventilation outside of the ICU treated with high-dose anakinra; the treatment was shown to be safe and it was associated with clinical improvement in 72% of the patients [32]. In a recently published cohort study by Huet et al. [33], including 52 patients in the anakinra group who were prospectively enrolled and 44 patients in the control group who were retrospectively selected, subcutaneous anakinra (100 mg twice a day for 72 h and then 100 mg daily for 7 days) reduced both the need for invasive mechanical ventilation in the ICU and mortality among patients with severe forms of COVID-19, without serious side effects [33]. Obviously, despite the promising results of these studies, controlled

trials are required in order to obtain confirmation of efficacy. Swedish Orphan Biovitrum, the manufacturer of anakinra, announced upcoming trials of anakinra in COVID-19 in a recent press release [34]. A small retrospective analysis of 10 patients treated with canakinumab, an IL-1β antibody (Novartis), 10 patients with severe COVID-19 pneumonia and hyperinflammation showed rapid improvement of the inflammatory response and resolution of the hypoxemia [35], supporting the central role of IL-1β and the inflammasome in COVID-19. A phase 3 clinical trial with canakinumab in severe COVID-19 disease is ongoing (NCT04362813).

### IL-6 Antagonists

Anti-IL-6 agents are a class of drugs with anti-inflammatory properties that act by targeting either the IL6 receptor or IL-6 itself. Studies have shown that tocilizumab, an IL-6 receptor antibody, could reverse CRS in the setting of chimeric antigen receptor T-cell therapy for cancer [36]. Because of the greatly elevated serum levels of IL-6 in patients with COVID-19 [3], its off-label used in the early stage of the diseases suggests a favorable impact on the course of COVID-19 [37]. Moreover, in 2 small retrospective studies of COVID-19 patients in China suffering from severe lung injury it was observed that the use of this agent could provide significant clinical improvement without important side effects [38, 39]. A press release from a network of hospitals in France announced that the CORIMUNO-TOCI (NCT04331808) trial of tocilizumab versus placebo in patients with severe COVID-19 pneumonia not requiring mechanical ventilation met the primary endpoint of reduction in the proportion of deaths or the need for mechanical ventilation at 14 days [40].

Another ongoing clinical trial (NCT04327388) aims to assess the efficacy of sarilumab, another IL-6 receptor inhibitor, in adult patients hospitalized with severe or critical COVID-19. A press release from Regeneron announced the results of the phase 2 study and the decision to proceed with enrollment in phase 3 only in patients defined as "critical," i.e., those requiring high-flow oxygen therapy or mechanical ventilation. The press release showed encouraging data for sarilumab (400 mg) versus placebo in the reduction of death or the need for ventilator on day 29, with intermediate results for the 200-mg arm, hence the decision to continue with only the 400-mg arm in phase 3 [41].

Furthermore, an ongoing clinical trial (NCT04380961) is evaluating the response to sirukumab, an antibody targeting IL-6, administered as a single intravenous dose, compared to placebo in severe or critical COVID-19 on top of standard of care.

A clinical trial (NCT04330638) is also testing whether combined IL-1 and IL-6 blockade using anakinra, tocilizumab, and siltuximab (another antibody that binds to IL-6), alone or in different combinations, may produce additional clinical benefits (in terms of death, days hospitalized, ICU days, etc.) compared to standard-of-care or single anticytokine therapy.

Tocilizumab is now already included in many practice guidelines for COVID-19 management, especially for the treatment of critically ill patients with severe refractory hypoxemia in a later stage after the high-viral-load initial phase all over the world, while we wait for more definite data from multiple ongoing clinical trials [42].

### TNF-α Blockers

The viral spike protein of SARS-Cov2 seems to induce a TNF-α-converting enzyme (TACE)-dependent alteration of ACE-2, which allows virus penetration into host cells, and the more TNF-α levels are increased the more this pathway is facilitated [43]. TNF antagonism in high cytokine states is a relatively unexplored field, with a case report suggesting a potential benefit in macrophage activation syndrome caused by herpes virus simplex infection [44]. A clinical trial evaluating the effects of the TNF-α blocker adalimumab in COVID-19 infection is currently ongoing (ChiCTR2000030089).

### Janus Kinase Inhibitors

The Janus kinase (JAK) family, and in particular the adaptor-associated protein kinase 1 (AAK1), plays a role in viral particles endocytosis; AAK1 inhibitors have been suggested as possible candidates for the treatment of COVID-19. Barcitinib, a JAK inhibitor with a high affinity for AAK1-binding, has been the first to be considered due to its relative safety [45]. However, there is the risk that JAK inhibitors could affect the activity of a variety of inflammatory cytokines, including INF-α, a potent mediator of the antiviral response. At present, there are 2 clinical trials (ChiCTR2000030170 and ChiCTR2000029580) the results of which will hopefully provide further insights into JAK and AAK1 inhibition effects in COVID-19 patients.

### C-C Chemokine Receptor Type 5 Inhibition

C-C chemokine receptor type 5 (CCR5) is expressed on the surface of white blood cells, especially T-CD4+ cells, and mediates macrophage migration into areas of inflammation, favoring the release of inflammatory cytokines and amplification of the immune response [46]. A phase 2 trial is currently evaluating leronlimab, a humanized monoclonal antibody inhibiting CCR5 which is already under study in HIV infection [46], to determine whether blockage of this pathway is able to reduce mortality at 28 days in severe forms of COVID-19 (NCT04347239).

## Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) possess potent immunomodulatory activities [47]. Several in vivo studies in animal models and ex vivo human lung models have proven that MSC can prevent lung injury, reduce inflammation, regulate immune responses, and foster alveolar fluid clearance [47]. Moreover, MSC secrete antimicrobial and painkiller molecules [47]. The in vivo safety of in vivo local and intravenous administration of MSC has been demonstrated in multiple human clinical trials, including studies of ARDS [47]. On the basis of these positive results, MSC use has been proposed to treat lung injury due to COVID-19, and a recent pilot trial by Leng et al. [48] including 7 patients showed that intravenous transplantation of ACE-2 MSC is safe and effective for the treatment of SARS-CoV2-related pneumonia, especially in patients in critically severe condition. At present, there are several ongoing clinical trials testing the application of mesenchymal stromal stem cells (SC) (NCT04361942 and NCT04345601), adipose-tissue-derived SC (NCT04366323), human dental pulp SC (NCT04336254), and bone marrow-derived SC in COVID-19 patients, which hopefully will provide further insight into the potential beneficial/harmful roles of MSC.

## Intravenous Immunoglobulin Therapy

Intravenous immunoglobulin (IVIg) has already been proven to be beneficial in patients with autoimmune and chronic inflammatory diseases [49, 50]. A new perspective is the use of IVIg-containing polyclonal immunoglobulin G (IgG) isolated and pooled from healthy donors to provide short- and medium-term therapies to COVID-19 patients [51]. IVIg may exert many anti-inflammatory and immunomodulatory effects which could accelerate virus clearance and prevent entry into target cells. In a small Chinese case series from Jin Yin-tan Hospital (Wuhan, China) a high dose of IVIg administered within the first few days of clinical deterioration proved to be a valuable option to block COVID-19 cascade progression, thus obtaining significant improvements in terms of clinical outcomes and recovery rates; the

timing, however, was found to be crucial, as no beneficial effects were observed if lung injury and systemic damage had already occurred [52]. Despite it being promising, IVIg use in COVID-19 requires evaluation in dedicated prospective and randomized clinical trials.

### Convalescent Plasma Therapy

Convalescent plasma therapy (CPT) is based on the transfusion of plasma collected from patients who have recovered from SARS-CoV2 infection, and developed antibodies, to susceptible individuals in order to confer them immediate immunity. Plasma from healthy donors provides neutralizing antibodies, limiting viral amplification and immunomodulatory effects via the infusion of anti-inflammatory cytokines and antibodies that block complement, inflammatory cytokines, and autoantibodies [53]. CPT has already been proven to be beneficial both as postexposure prophylaxis and/or treatment for different infectious diseases, including in the context of SARS-1 and MERS outbreaks [54]. Recently, in a case series of 5 critically ill patients with COVID-19-related ARDS, convalescent plasma transfusion with a SARS-CoV-2-specific antibody (IgG) [52] led to improvement in patients' clinical status. Moreover, a systematic review by Rajendran et al. [55] including 5 studies on the use of CPT in COVID-19 individuals showed that this therapy may reduce mortality in critically ill patients, increase neutralizing antibody titers, allow the disappearance of SARS-CoV-2 RNA in a large number patients, and lead to significant symptom relief. Of note, the CPT benefit is greater when it is used in a timely manner in the early viremic phase as its prevalent action is through direct neutralization of the virus, whereas the use of IVIg administration may be useful even in a more tardive phase as its principal mechanism is to counteract the deleterious effects of the dysregulated immune response. On the basis of these encouraging results, there are several ongoing clinical trials testing the efficacy of CPT in COVID-19 patients, and their results may provide further insights into the proper timing and modality of use of this promising therapy.

### Blood Purification

A nonpharmacological option for COVID-19 to counteract the dysregulated proinflammatory response could be represented by blood purification techniques [56, 57]. Nevertheless, the application of these techniques in COVID-19 patients is still not widespread and further investigation is needed to confirm their beneficial effects.

Therapeutic plasma exchange is an extracorporeal treatment performed by filtrating a volume of plasma equivalent to the estimated plasma volume that selectively removes circulating pathogenetic substances, such as auto-reactive antibodies, immune complexes, paraproteins, lipoproteins, and inflammatory mediators, like cytokines. Therapeutic plasma exchange was proven to be effective as rescue therapy to mitigate the cytokine storm in a small case series of patients suffering from pH1N1 influenza A-associated respiratory failure and hemodynamic shock, reducing the need for vasopressors and improving the $PaO_2/FiO_2$ ratio [58].

Hemadsorption is performed using dedicated blood adsorber devices, with a highly porous biocompatible polymer able to bind hydrophobic compounds with a molecular weight between 10 and 55 kDa, a range where most cytokines reside. In Europe Cytosorb© cartridges (CytoSorbents Corporation, USA) are among the most diffused extracorporeal therapies with the aim of obtaining cytokine blood purification, and it has been proven to be beneficial in controlling the dysregulated inflammatory response in patients who have undergone cardiac surgery or are critically ill [59]. In a case series of septic patients requiring renal replacement therapy, an adjunctive hemoadsorption strategy resulted in rapid hemodynamic stabilization and a sensible

decrease in blood lactate, with a reduction of the mortality rate compared to the mortality rate predicted by acute physiology and chronic health evaluation II (APACHE II score), especially when started within 24 h of a sepsis diagnosis [60]. This approach provides a nonspecific cytokine removal, thus leading to the assumption that the possible underlying mechanism explaining its efficacy lies in the fact that cytokines that are more concentrated and, therefore, more likely to be harmful are eliminated to a greater extent [59]. Moreover, according to the "cytogenetic model," clearance of circulating cytokines could allow redirection of the host immune response to the source or sites of inflammation [61]. Nevertheless, at present, cytokine hemoadsorption therapy is not a standardized strategy and there is still a lack of control trials proving its real effectiveness in clinical outcome improvement and short- and long-term survival in humans. Further research is needed to clarify the mechanisms of action, indications, and clinical benefits of this therapy [19, 62]. However, in the absence of resolutive options for COVID-19 treatment, the use of hemoadsorption therapies in critical cases has recently been proposed, as it could help to contain the inflammatory response responsible for CRS in these patients.

Another adjunctive potential of extracorporeal therapy includes plasmapheresis using high-affinity matrixes of lectin for coronavirus trapping, thus leading to a viremia reduction [63].

In patients who fail other treatments, extracorporeal membrane oxygenation (ECMO) remains the last resource [64]. An ongoing trial (NCT04324528) is currently testing whether veno-venous (vv) ECMO in combination with a cytokine adsorption (Cytosorb adsorber) device, versus vv-ECMO alone may blunt inflammation parameters and improve patient survival in those with severe COVID-19 infection.

Recently, a small case series of COVID-19 patients treated with blood purification therapies showed a reduction of inflammatory markers, and 2 out of 3 patients survived with no early complications [65]. Nevertheless, the high cost and relatively low availability represent a significant limitation for the use of this option for a pandemic viral disease, highlighting the need to accurately select the target patients.

## Future Perspectives

In the COVID-19 pandemic, the timing and patient selection will be crucial issues to handle limited and often expensive resources, and an integrated multimodality approach of clinical, laboratory, and imaging parameters may help to guide the management of these patients. Identification of patients with a hyperinflammatory response through cytokine profiling could direct the choice of a specific anticytokine drug or even combined/sequential regimens; if these prove ineffective in improving the clinical status, implementation of broad-spectrum anti-inflammatory therapies, such as IVIg and blood purification, could be considered. However, before starting therapeutic regimens including immunosuppressive drugs, it is of paramount importance to take into account the risk of previous viral infection (i.e., HBV, HCV, EBV, and VZV), tuberculosis, and histoplamosis reactivation, and, accordingly, to consider concomitant antiviral/antifungal prophylaxis.

## Conclusions

In the quest for more effective COVID-19 therapeutic strategies, accumulating evidence suggests the role of immune system dysregulation leading to an inappropriate CRS in the pathogenesis of progressive hypoxia in patients with COVID-19. While the initial results with immune modulators are promising, the results of ongoing clinical trials will clarify the efficacy, safety, and role of the different treatments according to disease stage and severity.

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## Conflict of Interest Statement

C.R. in the last 3 years has been consultant, speaker, or advisor for Astute, Asahi, Biomerieux, Baxter, FMC, B. Braun, Cytosorbents, GE, Medtronic, and Jafron. All of the other authors have no relationship relevant to the contents of this paper to disclose.

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