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Cytokine Storm in COVID-19: "When You Come Out of the Storm, You Won't Be the Same Person Who Walked in"

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In December 2019, a novel coronavirus, COVID-19, was discovered to be the causal agent of a severe respiratory infection named SARS-CoV-2, and it has since been recognized worldwide as a pandemic. There are still numerous doubts concerning its pathogenesis and particularly the underlying causes of the various clinical courses, ranging from severe manifestations to asymptomatic forms, including acute respiratory distress syndrome. The major factor responsible for acute respiratory distress syndrome is the so-called "cytokine storm," which is an aberrant response from the host immune system that induces an exaggerated release of proinflammatory cytokines/chemokines. In this review, we will discuss the role of cytokine storm in COVID-19 and potential treatments with which counteract this aberrant response, which may be valuable in the clinical translation.

Keywords: cytokines, SARS-CoV2, inflammation, coronavirus, acute respiratory distress, severity

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INTRODUCTION

For the third time, a zoonotic coronavirus has crossed species boundaries to infect humans. Initially, the virus was detected in people exposed to seafood. First reports revealed that human-to-human transmission was impossible or restricted; it is now clear that such transmission occurs, though the underlying mechanisms are still unclear (1). In December 2019, this coronavirus was detected for the first time in the respiratory tract of patients with pneumonia in Wuhan, Hubei, China, and it was identified as a new β-coronavirus (nCoV). This novel coronavirus was subsequently named as Coronavirus-2 disease (COVID-19), and it leads to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 has afflicted about 5 million people worldwide, and it was recognized as a pandemic by the World Health Organization (WHO) in March 2020 (2, 3).

The effect of COVID-19 can encompass anything from asymptomatic disease to critical infection, with 661,244 deaths reported worldwide to date (July 31, 2020) (4) and more than 30% of hospitalized patients needing mechanical ventilation in intensive care units (5, 6). Death rates depends on aging and presence of comorbidities (including obesity, diabetes, cardiovascular problems, cancer and hypertension) (5, 7). Patients with severe COVID-19 showed multi-organ failure and rapid advancement of lung infiltrates, which is concomitant with a sustained release of inflammatory cytokines and biochemical makers of inflammation. The cytokine storm could be on the basis of the difference between asymptomatic and patient with severe symptoms (6, 8–11). So far, seven human coronaviruses have been found, comprising α-types (HCoV-229E and HCoV-NL63), β-types [SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), HCoV-HKU1, and HCoV-OC43] and the present 2019-nCoV epidemic. Regarding their

pathogenicity, human coronaviruses are divided into being moderately and severely pathogenic, and these include SARS-CoV (12), MERS-CoV (13), and SARS-CoV-2 (14). The entire human population lacks immunity to SARS-CoV-2 and is thus susceptible to the novel coronavirus. To date, no exhaustive studies have been reported about the immune host response to SARS-CoV-2, and we consequently need to relate to previous findings on other CoVs.

ABERRANT HOST IMMUNE RESPONSE

The underlying mechanisms of severe infection in patients affected by SARS-CoV-2 are still unclear, and the progress of the severe form does not seem to be exclusively related to a viral titer and may include defective interferon responses (15). An excessive inflammatory response to SARS-CoV-2 represents the main cause of disease severity and death in COVID-19 patients (16), and it is characterized by acute lymphopenia, elevated levels of circulating cytokines, and substantial mononuclear cell infiltration in the lungs, spleen, kidneys, lymph nodes (6), and heart (17), as revealed in post-mortem exams.

It is well-known that cytokines perform a key function in the immunopathology during viral infection. The first response against viral infection is a synchronized and fast innate immune reaction. Extreme and uncontrolled immune reactions may, however, trigger immune impairment in the human body (18–20). In patients affected by SARS-CoV-2, the proinflammatory response and, in particular, the cytokine storm represent a centerpiece of COVID-19 pathogenesis, causing great destructive consequences for the host. When the immune system is not more able to counteract the virus and to conclude the inflammatory response, the aberrant production of the cytokines led to macrophage hyperactivity, with consequences for the whole body, including fever, anemia, and organs malfunction. At some point, the cytokine storm becomes unstoppable, leading to irreversible end-organ dysfunction and even death (21, 22).

In vitro studies reported that, at the initial phase of SARS-CoV infection, a delayed release of chemokines and cytokines appeared in macrophages, airway epithelial cells, and dendritic cells. In the following phases, cells secrete elevated quantities of proinflammatory cytokines (including interleukins and tumor necrosis factor) and chemokines [C-C motif chemokine ligand (CCL)2, 3 and 5], which is in parallel with low quantities of antiviral factors interferons (INFs) (23–26).

Like SARS, MERS coronavirus infects human respiratory epithelial cells, dendritic cells, and peripheral blood monocyte-derived macrophages, inducing delayed but elevated quantities of chemokines and proinflammatory cytokines (25, 27). In the following stages of the infection, plasmacytoid dendritic cells, but not dendritic cells and mononuclear macrophages (28), are induced to produce a large amount of IFNs. Indeed, serum chemokine and cytokine levels are considerably more elevated in patients with severe MERS than patients with moderate MERS (29), associated with higher number of monocytes and neutrophils in lung tissues and blood of these patients; these cells may thus be involved in the pathogenesis (26, 30). Comparable events have been reported in patients with SARS-CoV infection (26, 31–33).

The delayed release of IFNs during the infection impedes immune system activation against the virus (18). Subsequently, the rapid increase in cytokine and chemokine release stimulates different inflammatory cells, including monocytes and neutrophils, causing an excessive infiltration of the inflammatory cells into lung tissues with consequent lung damage. An over-response of the infected cells seems to be at the basis of MERS or SARS pathogenesis.

Animal models help dissect the role of chemokines and cytokines in the immunopathology after coronavirus infection. Notably, SARS-CoV-infected old non-human primates showed higher probability of developing an excessive inflammatory response compared to young primates characterized by more severe pathology (34). The immune overreaction rather than virus titer is crucial in determining the old non-human primates death (34). Comparably, BALB/c mice infected with SARS-CoV showed higher severity in old mice, which is associated with early and strong upregulation of the acute respiratory distress (ARDS)-related inflammatory gene signals (35). The fast replication of SARS-CoV in these animals leads to the delayed release of IFNs in parallel with the invasion of various mononuclear macrophages (18). These macrophages receive activating signals through the IFN-α/β receptors on their surface and release monocyte chemoattractants (such as CCL2, CCL5, and CCL7), resulting in the additional accumulation of mononuclear macrophages. Furthermore, mononuclear macrophages stimulate higher release of proinflammatory cytokines [ILs and Tumor Necrosis factor (TNF)], thus increasing the severity of the disease. Indeed, it has been demonstrated that neutralizing TNF or reducing the inflammatory macrophages in mice protected from SARS-CoV infection, and INFs or macrophages led to T-cell apoptosis, ulteriorly preventing viral infection (18). In the light of this, it has been postulated that COVID-19 showed similar behavior to other CoVs.

ACUTE RESPIRATORY DISTRESS

Since the first reports on COVID-19 disease, it appeared clear that ARDS has led to a relevant number of deaths among infected patients. ARDS should be considered an immune-mediated clinical consequence in SARS-CoV-2, similarly to what described for SARS and MERS infections (17).

The "cytokine storm" concept is derived from the observation that COVID-19 patients requiring intensive care unit admission presented elevated circulating concentrations of CXCL10, CCL2, and TNFα as compared to those in which the infection was mild or moderate (36, 37).

Furthermore, elevated levels of IL-1, IFN-γ, IP-10, and monocyte chemoattractant protein 1 (MCP-1) have been detected in patients with COVID-19. These inflammatory cytokines may

stimulate the T-helper type 1 (Th1) cell activation (38). The Th1 response is a crucial event in the immune system response (39). In contrast to SARS patients, however, individuals affected by COVID-19 also showed higher levels of Th2 cell-secreted cytokines (i.e., IL-4 and IL-10), which inhibit the inflammatory response. Serum levels of these cytokines in COVID-19 patients are related to higher severity the disease (26). In addition, COVID-19 patients in intensive care units showed elevated serum levels of granulocyte colony-stimulating factor, IP-10, TNF-α, MCP-1, and macrophage inflammatory protein 1A respective to patients from general areas (38). The cytokine storm occurred in response to SARS-CoV-2 infection and induced the upregulation of Natural killer group 2 on Natural Killer and cytotoxic T cells. This increase inhibited the function of these cells and counteracted cytokine release (40–42).

Another effect of the fast-viral replication and of the strong proinflammatory response is the induction of apoptosis in pulmonary endothelial and epithelial cells. In particular, IFNs cause inflammatory cell infiltration through mechanisms, including TRAIL (TNF-related apoptosis-inducing ligand)–death receptor 5 and Fas–Fas ligand (43–45).

Lung endothelial and epithelial cell apoptosis damages the respiratory microvascular and alveolar epithelial cell barriers, leading to alveolar edema, vascular leakage, and, finally, causing hypoxia in the entire body. Consequently, inflammatory mediators are at the basis of the pathogenesis of ARDS. ARDS is the primary cause of mortality in patients affected by SARS-CoV or MERS-CoV (46, 47). It is known that several proinflammatory cytokines (IL-6, IL-8, IL-1β, and granulocyte-macrophage colony-stimulating factor), chemokines [such as CCL2, CCL5, IFNγ-induced protein 10 (IP-10), and CCL3], and reactive oxygen species all participate in the development of ARDS (48–50).

After SARS-CoV infection, a high virus load and exaggerated immune response lead to an inflammatory cytokine storm, accompanied by immunopathological alterations in the lungs and then in other organs. ARDS and multi-organ malfunction appeared quickly, leading to death within a short period (51). Overall, the cytokine storm is considered to be one of the main causes of ARDS and multi-organ failure (52).

ARDS pathogenesis implicates inflammatory damage to the alveolus–capillary membrane, with consequent improved pulmonary permeability and elevated exudation of protein-rich fluid into the airspaces, inducing respiratory insufficiency. Current management of COVID-19 is supportive, and respiratory failure from ARDS is the leading cause of death (16, 53). Secondary hemophagocytic lymphohistiocytosis (sHLH) is an under-recognized hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiple-organ failure. In adults, sHLH is most commonly triggered by viral infections (54) and occurs in about 4% of sepsis cases (55). Key characteristics of sHLH, comprising chronic fever, hyperferritinemia, cytopenia, and pulmonary involvement (including ARDS), appeared in approximately 50% of patients (56). A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterized by increased IL-2, IL-7, granulocyte-colony stimulating factor, INF-γ inducible protein 10, CCL1, macrophage inflammatory protein 1-α, and TNF-α (38).

A recent retrospective, multicenter study of 150 confirmed COVID-19 Chinese patients revealed that predictors of mortality involved higher IL-6 and ferritin levels (mean 1,297.6 ng/ml in non-survivors vs 614.0 ng/ml in survivors) (53), indicating that the disease lethality may be due to virally driven hyperinflammation.

A report on SARS-CoV-2 showed that more than 70% of affected patients needed mechanical ventilation, and about 67% suffered from ARDS. Additionally, the number of death of the elderly patients with ARDS was considerably higher (57). As we mentioned above, the main variation in ARDS is the pulmonary and interstitial tissue injury due to non-specific cell infiltration, and the pivotal factor is the local excessive cytokine release, which has lead to pathological alteration in the whole body and clinical symptoms (37, 58).

The cytokine storm is thus at the basis of the onset and progression of ARDS. The serum levels of cytokines are considerably elevated in these patients, and the degree is clearly associated with death rate (16). The cytokine storm is also at the basis of the clinical progression of extrapulmonary multi-organ collapse (37, 59). This partly explicates the extra-pulmonary organ failure (i.e., elevated liver enzymes and creatinine) found in a few COVID-19 patients that do not show respiratory problems, indicating that the cytokine storm is the trigger of extrapulmonary injuries in tissues and organs.

In summary, the new coronavirus infection leads to an inflammatory cytokine storm in the affected patients. The cytokine storm, in turn, triggers ARDS and multi-organ failure and represents a crucial factor in COVID-19 exacerbation or even mortality (**Figure 1**).

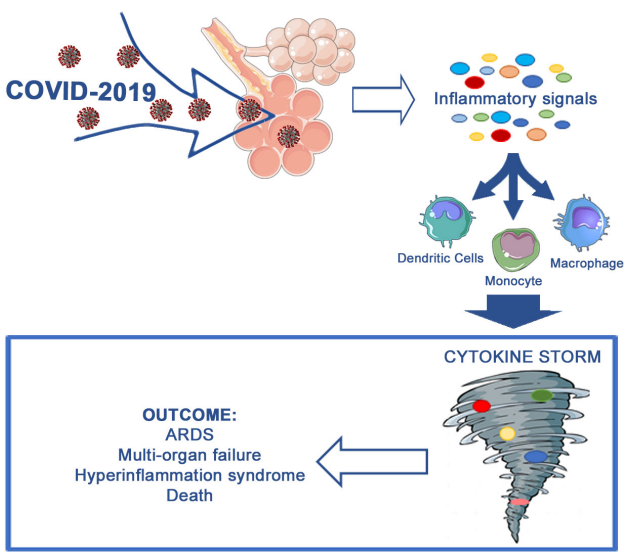

FIGURE 1 | Aberrant immune host response occurring during COVID-19 infection.

However, the main question is why some patients are more predisposed to cytokine storm respect others. Different genetic mutations may also represent a risk factor for the severe disease course and the occurrence of cytokine storm in COVID-19. Notably, data obtained from a global population indicate that allelic alterations in cytokine genes showed a sharp latitudinal impact (60, 61). Geographical latitude is the main environmental factor that is affected by our evolutionary history with respect to environmental selection. The latitude is therefore associated with a variety of factors comprising genetic background, biometeorological factors, and socio−economic influences. Regarding the role of biometeorological factors, the sunlight has a pivotal role for the synthesis of Vitamin D, which in turn plays a key role in preserving the immune homeostasis. Genetic factors are known to account for up to 28% of inter−individual variability in serum 25(OH)D concentrations (62). Genetic as well as individual differences of vitamin D status have been reported across various populations (63). In the light of this, we can postulate that there is a possibility that vitamin D status may have some influence on geographical variance of COVID−19.

Furthermore, deficiency in vitamin D may lead to increased autoimmunity and elevated susceptibility to infections. Indeed, Vitamin D inhibit the production of proinflammatory cytokines (i.e., TNF−α and IFN−γ) and stimulate the release of anti−inflammatory cytokines. Vitamin D decreases the risk of microbial infection and death through different mechanism. A recent review categorized those mechanisms into three groups, including a physical barrier as well as innate and adaptative immunity (64). COVID-19 viruses disrupt junction integrity, increasing the susceptibility to the infection by the virus and other microorganisms (65), while vitamin D supports the maintenance of cell junctions integrity (66). Vitamin D may be valuable in controlling the cytokine storm and the outcome of COVID−2019 patients. Its deficiency leads to greater risk, and supplements of Vitamin D could thus be potentially used (67).

Cytokine regulation, however, depends on different upstream regulators, such as Toll-like Receptors (TLRs), and these interrelate with other components of innate immune system, such as complement elements. TLRs are a family of innate immune sensor proteins exerting a key function in infection, inflammation and immunity processes (68); TLR pathway may be significantly implicated in cytokine storm occurring during COVID-19 infection. To date, there are no studies regarding the role of TLR signaling in SARS−CoV−2 infection. Previous studies indicate, however, that genetic variation within TLRs or TLR signaling affected SARS−CoV infection (62, 68–71).

Moreover, the complement system interacts with TLRs, and it is thus involved in higher susceptibility to the infection and cytokine storm activation (72). In fact, a recent study reported that the complement system represents a crucial host mediator of SARS−CoV infection. SARS−CoV−infected $C3^{-/-}$ mice exhibited less respiratory impairment and lowered levels of chemokines and cytokines in the organs (73). In addition, hyperactivation of the complement system was reported in COVID−19 patients, and the highly pathogenic coronavirus N protein exacerbated MASP−2−mediated complement activation (74). Overall, the complement system is crucially involved in the stimulation of the cytokine storm and inflammation in SARS−CoV−2 infection.

COVID-19 EXPERIMENTAL AND CLINICAL INVESTIGATIONS

Data concerning the correlation between COVID-19 and cytokine/chemokine dysregulation are still limited, but the current available *in vitro* and clinical studies suggest a likeness with what was reported after SARS and MERS infections.

So far, few studies into SARS-CoV-2 infection have been reported. One interesting study compared SARS-CoV-2 and SARS-CoV behavior in the pulmonary tissue. The research group inoculated the viruses in *ex vivo* human pulmonary tissue samples and reported that SARS-CoV-2 was more efficient than SARS-CoV in both replicating and infecting human lung tissues. Additionally, SARS-CoV-2 infection was less competent in inducing the expression of any IFNs, suggesting that SARS-CoV and SARS-CoV-2 may differ in their capability to control proinflammatory cytokines and chemokines release. Indeed, SARS-CoV infection increased 11 out of the 13 proinflammatory factors tested in this study, while SARS-CoV-2 upregulated only five of them (i.e., CXCL10, IL6, CCL2, CXCL1, and CXCL5) despite replicating more efficiently. The expression of 12 out of 19 among IFNs and cytokines/chemokines genes tested was substantially lower in SARS-CoV-2-infected human samples than SARS-CoV-infected samples. Notably, CXCL8 transcription was increased only by SARS-CoV, but not SARS-CoV-2 infection, while the opposite for CXCL10 was detected (75).

Another research group isolated SARS-CoV-2 from a patient with established COVID-19 and compared virus tropism and replication competence with SARS, MERS, and 2009 pandemic influenza H1N1 (H1N1pdm) in *ex vivo* samples of human lung and bronchus. To assess extrapulmonary infection, the authors used *ex vivo* cultures of human conjunctiva epithelium (potential portals of infection for SARS-CoV-2) and human colorectal adenocarcinoma cell lines (17). SARS-CoV-2 was able to infect mucus-secreting, ciliated, and club cells of bronchial epithelium type 1 pneumocytes in the lung and the conjunctival mucosa. In the bronchus, SARS-CoV-2 replication was higher than SARS and similar to MERS and lower than H1N1pdm. In the lungs, SARS-CoV-2 replication was comparable to SARS and H1N1pdm but lower than MERS. In conjunctiva, SARS-CoV-2 replication was superior to SARS-CoV. SARS-CoV-2 was less effective in inducing proinflammatory cytokines than H1N1 and MERS. Both SARS-CoV and SARS-CoV-2 are thus comparably replicated in the alveolar epithelium; SARS-CoV-2 is replicated more extensively in the bronchus than SARS-CoV. These findings support valuable insights into the transmissibility of SARS-CoV-2 infection and dissimilarities with other respiratory pathogens (76).

In a retrospective study, the clinical and immunological features of 21 patients (17 male and four female) affected by COVID-19 were evaluated. These patients were classified in

different degrees of severity, according to the guidelines of the National Health Commission of China. In particular, the 11 patients with severe form exhibited considerably elevated serum levels of IL-6, IL-10, and TNF-α in parallel to the reduced absolute number of T lymphocytes, CD4 + T cells, and CD8 + T cells with respect with moderate cases. This retrospective observational study suggests that SARS-CoV-2 infection may involve principally T lymphocytes, particularly CD4 + and CD8 + T cells, leading to decreased T lymphocytes number as well as IFN-γ production by CD4 + T cells. These potential immunological markers can be relevant due to their association with COVID-19 disease severity (6).

To characterize the transcriptional signatures of host inflammatory response to SARS-CoV-2, Xiong and collaborators performed a transcriptome sequencing of different proinflammatory genes from RNAs isolated from the broncho-alveolar lavage fluid and peripheral blood mononuclear cells of COVID-19 patients. This analysis showed distinct host inflammatory cytokine profiles to SARS-CoV-2 infection and supports the association between COVID-19 pathogenesis and aberrant cytokine release; CXCL10 in particular was upregulated in peripheral blood mononuclear cells, but no up-regulation of CXCL10 gene in broncho-alveolar lavage fluid was detected. Additionally, SARS-CoV-2 induced the activation in lymphocytes of numerous genes involved in apoptosis and P53 pathways, leading to the assumption that this activity may be the primary cause of lymphopenia frequently detected in COVID-19 cases. The transcriptome sequencing analysis of COVID-19 patients represents a significant source for clinical guidance on anti-inflammatory treatment and to understand the molecular mechanisms of host response (77).

Another study, involving 65 SARS-CoV-2-positive patients, revealed that the absolute numbers of CD4 + and CD8 + T cells and B cells progressively diminished in relation to increased severity of disease (78). Furthermore, Yang and collaborators analyzed 48 circulating cytokines from 53 COVID-19 patients (34 severe cases), and 14 resulted higher in patients with severe COVID-19 clinical history. Among them, CXCL10, CCL7, and IL-1 receptor antagonist were the ones strongly related to severity illness and, even more significantly, CXCL10 levels were the only one to be positively and significantly correlated with the viral load (79).

In 70 patients who survived severe COVID-19 pneumonia, 66 showed significant damage as revealed by CT scans taken before hospital release. The injury varied from dense clumps of tissue obstructing blood vessels of the alveoli to tissue lesions. The tissue lesions may represent signs of chronic lung disease and may be irreversible, rendering the patient frail (80). Furthermore, people who survived ARDS due to COVID-19 may have lasting pulmonary scarring (81). If pulmonary tissues are replaced with scar tissues, they are no longer functional as normal lung tissues, which may lead to poor gas exchange. Similar damage has been documented also in survivors of MERS and SARS even if those illnesses attacked only one lung.

Many patients hospitalized for COVID-19 also face cardiovascular problems, with unexpectedly high rates of blood clots, due to inflammatory reactions to this infection that lead to stroke, heart attack, lung blockages, neurological problems, and other complications with serious and lasting effects (82–86).

POTENTIAL TREATMENTS

The use of glucocorticoids represents one of the approaches to treat COVID-19 patients (87). The dosage and timing of administration are crucial to the outcome, especially of severe cases. Indeed, a too early administration of glucocorticoids impedes the immune system activation, thus enhancing the viral cargo and increasing the adverse effects. Consequently, glucocorticoids are mostly utilized in critical COVID-19 patients experiencing an inflammatory cytokine storm.

The inhibition of the aberrant inflammation through timely administration of glucocorticoids in the early stage of an inflammatory cytokine storm may efficiently inhibit ARDS onset and preserve the organs functions. For cases with progressive worsening of oxygenation indicators, rapid imaging progress, and aberrant inflammatory response, the use of glucocorticoid in the short term (3–5 days) is suitable, and the recommended dose is no more than equivalent to methylprednisolone 1–2 mg/kg/day (87). On the contrary, glucocorticoid at high dosage may impede the clearance of COVID-19 due to immunosuppression.

Notably, cytokines inhibition approaches are presently being investigated for COVID-19 treatment, and hydroxychloroquine, a long-known drug used as treatment of immune-mediated inflammatory diseases, showed high efficacy, reducing the time to clinical recovery and helping the absorption of pneumonia, as reported in a randomized clinical trial (88). Furthermore, it was able to prevent the release of TNF and IL-6 (89). Chloroquine phosphate has been used in the treatment of adults aged 18–65 in China (90). Based on ongoing analysis and emerging scientific data, however, the Food and Drug Administration (FDA) has revoked the emergency use authorization (EUA) to use chloroquine and hydroxychloroquine to treat COVID-19 in specific hospitalized patients under careful heart monitoring. FDA made this decision based on recent findings from a large, randomized clinical trial in hospitalized and non-hospitalized patients that revealed that these drugs had no benefit for improving the recovery and decreasing the death (91, 92).

During the cytokine storm, the most relevant cytokines are the IL-1 family; studies that focus on the inhibition of IL-1β to counteract the cytokine storm attracted most attention. Interestingly, Anakinra, an antagonist of IL-1β, radically ameliorated the survival rate of patients with severe sepsis (93). However, there are no clinical studies to treat COVID-19 using specific IL-1 family blockers, and *in vivo* studies and clinical trials are thus necessary.

Regarding the other ILs, Tocilizumab, a humanized anti-IL-6 receptor IgG monoclonal antibody applied as treatment for chronic inflammatory diseases, was used as treatment option to better understand the underlying molecular mechanism of aberrant cytokine response in COVID-19 pneumonia and to define the clinical effects. In a very recent study, upon use of Tocilizumab, 83% of cases showed remarkable clinical and

laboratory ameliorations, while 17% of the patients needed short-term ventilator assistance in the intensive care unit. This study suggested that Tocilizumab (administered at the right time) is valuable in inhibiting the injury caused by aberrant cytokine response and offers clinical and radiological recovery. Indeed, upon use of Tocilizumab, all patients showed normalized arterial oxygen saturation levels and the eosinophil values increased significantly in response to the treatment (94). Furthermore, Tocilizumab impedes the IL-6-mediated signal transduction by blocking the IL-6 receptor interaction. Clinical data on the use of Tocilizumab in COVID-19 cases are still limited; however, some authors propose its use in SARS-CoV-2 patients with elevated IL-6 levels (36, 37).

Another drug tested for COVID-19 was Sarilumab, an IL-6R antibody. There are contrasting data regarding its therapeutic potential. For instance, an observational study reported that IL-6R inhibitors, administered prior 45% FiO_2 (fraction of inspired oxygen) requirement, improved Covid-19 outcomes (95). On the other hand, recently, leading companies announced that the US Phase 3 trial of Sarilumab (400 mg) in COVID-19 patients requiring mechanical ventilation did not meet its primary and key secondary endpoints. In particular, minor positive trends that did not reach statistical significance were observed in the primary pre-specified analysis group (critical patients mechanically ventilated at baseline), and these were opposed by negative trends in a subgroup of critical patients who were not mechanically ventilated at baseline. Serious adverse effects that occurred in at least 3% of patients upon Sarilumab treatment were multi-organ failure syndrome and hypotension. Based on these results, the trial has been stopped (96).

CONCLUSION

Aberrant immune host response together with cytokine storm and lymphocytopenia, followed by ARDS, are still relevant problems that affect the severity of COVID-19, and the modulation of the immune response and inflammation may thus be considered as crucial. Although the above-mentioned therapeutic approaches presented encouraging results, further studies are necessary in order to better understand the immune response and immunopathogenesis occurring during COVID-19 infection. Moreover, in the light of the reported studies, many people that have contracted the COVID-19, also after recovery, need to be considered as frail patients, especially the ones in which ARSD and consequent multi-organ failure occurred.

AUTHOR CONTRIBUTIONS

VC wrote the manuscript upon CF supervision. VC prepared the figure. AC substantially revised the manuscript. All authors contributed to the article and approved the submitted version.

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