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Lung under attack by COVID-19-induced cytokine storm: pathogenic mechanisms and therapeutic implications

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***Abstract*:** The lung is a key target of the cytokine storm that can be triggered by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), responsible for the widespread clinical syndrome known as coronavirus disease 2019 (COVID-19). Indeed, in some patients, SARS-CoV-2 promotes a dysfunctional immune response that dysregulates the cytokine secretory pattern. Hypercytokinemia underlies the hyperinflammatory state leading to injury of alveolar epithelial cells and vascular endothelial cells, as well as to lung infiltration sustained by neutrophils and macrophages. Within such a pathogenic context, interleukin-6 (IL-6) and other cytokines/chemokines play a pivotal pro-inflammatory role. Therefore, cytokines and their receptors, as well as cytokine-dependent intracellular signalling pathways can be targeted by potential therapies aimed to relieve the heavy burden of cytokine storm. In particular, the anti-IL-6-receptor monoclonal antibody tocilizumab is emerging as one of the most promising pharmacologic treatments.

The reviews of this paper are available via the supplemental material section.

Keywords: ARDS, COVID-19, cytokine storm, immunomodulatory drugs, SARS-CoV-2, pneumonia

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Introduction

Immune responses, clinical presentations, and radiological patterns are quite heterogeneous among the multitude of people affected by the widespread COVID-19 syndrome.[1] One of the worst scenarios is sustained by the so-called cytokine storm, historically labelled as secondary haemophagocytic lymphohistiocytosis (sHLH), which is a complication most commonly encountered in viral infections.[2] Influenza viruses, Ebola virus, cytomegalovirus and, more recently, SARS-CoV-2 have been implicated in triggering the cytokine storm.[3] This cytokine storm may provide the possible mechanism on why certain subpopulations are more likely to die of COVID-19 than others.

When the immune system mounts an effective adaptive response against SARS-CoV-2, the infection can be cleared and clinical manifestations are absent or prone to complete recovery. This successful result is mediated by an antiviral $CD4^+$ T helper (Th) cell commitment, associated with activation of $CD8^+$ cytotoxic T lymphocytes and with a B cell-driven response leading to the production of specific antibodies.[4] However, when the human organism fails to develop an adequate adaptive immune reaction, viral persistence and the consequent prolongation and amplification of innate immune mechanisms, associated with dysfunctional adaptive responses, can cause a 'hyperinflammatory' state underlying the cytokine storm typical of acute respiratory distress syndrome (ARDS).[5] In other words, the massive and continuous release of proinflammatory cytokines and chemokines is responsible for a severe, even deadly, attack against the lung. Besides the comorbidities (respiratory, cardiovascular, metabolic, oncologic, etc.) involved, the senescence of the immune system plays a role in the worst outcomes observed in the elderly.[6,7] During childhood and

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adolescence, there are instead very high numbers of naïve T lymphocytes, ready to differentiate and to engage a successful fight against eventual new pathogens.[5] Indeed, children are currently paying a very low death toll to SARS-CoV-2 infection.

On the basis of the above considerations, the present review will focus on the pathogenic mechanisms underpinning the lung damage induced by the cytokine storm triggered by SARS-CoV-2, as well as on potential therapies targeting such a very severe condition.

Pathobiology of SARS-CoV-2-induced cytokine storm

Mechanisms of viral infection

SARS-CoV-2 is an enveloped, positive-sense and single-stranded RNA β-coronavirus, similar to coronaviruses responsible for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[8,9] Its nucleocapsid consists of genomic RNA and a phosphorylated N protein, which is embedded within phospholipid bilayers and surfaced by two spike proteins.[10] The latter include the spike glycoprotein trimmer (S) and the hemagglutinin-esterase (NE), among which the type III transmembrane glycoprotein M and the envelope E protein are interposed.[10] The S glycoprotein binds to the cell membrane receptor angiotensin-converting enzyme 2 (ACE2), expressed within the lower respiratory tract by type 2 alveolar epithelial cells.[11,12] This key function of S glycoprotein is primed by TMPRSS2, a human type 2 transmembrane serine protease, which thus facilitates virus entry into host cells.[11] The S glycoprotein comprises a S1 subunit mediating the cellular tropism of SARS-CoV-2, and a S2 subunit that is responsible for virus-cell membrane fusion.[13] This fusion is followed by penetration of viral genomic RNA into the cytoplasm. Once inside target cells, single-stranded viral RNA is recognised by the intracellular Toll-like receptor 7 (TLR7) located in endosomes.[14] As a consequence of this infectious process, SARS-CoV-2 RNA drives the translation and assembly of viral proteins inside the endoplasmic reticulum and Golgi apparatus. The newly formed vesicles, which contain viral particles, fuse with cell membrane thus releasing the virus.

Lymphopenia and lymphocytes exhaustion: a consequence of impaired adaptive immunity

Tissue destruction spreads throughout SARS-CoV-2-infected cells, which trigger innate immune responses mediated mostly by macrophages. Indeed, tight intercellular communications occur between ACE2-expressing lung epithelial cells and macrophages.[15] Within the context of class I major histocompatibility complex (MHC-I), macrophages present viral antigens to T lymphocytes, thereby leading to T cell subset commitment and activation.[16] The subsequent Th1-featured adaptive immune response should contribute to clear viral infection *via* the release of antiviral cytokines such as type I interferons (IFNs). However, it has been previously reported that severe infections caused by SARS coronavirus may be associated with low levels of IFN production.[17] Therefore, this pathobiologic scenario could be characterised by polarisation towards an aberrant T cell lineage and a dysregulated cytokine secretory pattern.

Indeed, it has been shown recently that SARS-CoV-2 infection can prime $CD4^+$ T lymphocytes to differentiate into pathogenic Th1 cells, secreting high amounts of interleukin-6 (IL-6) and granulocyte macrophage-colony stimulating factor (GM-CSF) (Figure 1).[18] Such a cytokine milieu promotes activation of $CD14^+$ $CD16^+$ monocytes, which in turn release IL-6 and may migrate from blood to lung, thus possibly becoming alveolar macrophages or dendritic cells (Figure 1).[18] In addition, severely ill COVID-19 patients develop dysfunctional immunophenotypes of $CD4^+$ and $CD8^+$ T lymphocytes, characterised by a high co-expression of surface markers such as PD-1 (programmed cell death protein-1) and Tim-3 (T-cell immunoglobulin and mucin-domain containing-3), which predisposes to a rapid T cell exhaustion during viral infections.[19–22] In fact, in patients with severe disease, innate immune mechanisms can fail to induce an effective virus-targeted cytotoxic response, normally implemented by activated $CD8^+$ cells.[23] Furthermore, the adaptive immune response induced by SARS-CoV-2 might be also shaped as a predominant Th17 profile.[24]

Hypercytokinemia in COVID-19

Cross-talking innate and adaptive immune pathways lead lung epithelial cells, activated monocytes/macrophages and T lymphocytes to massively

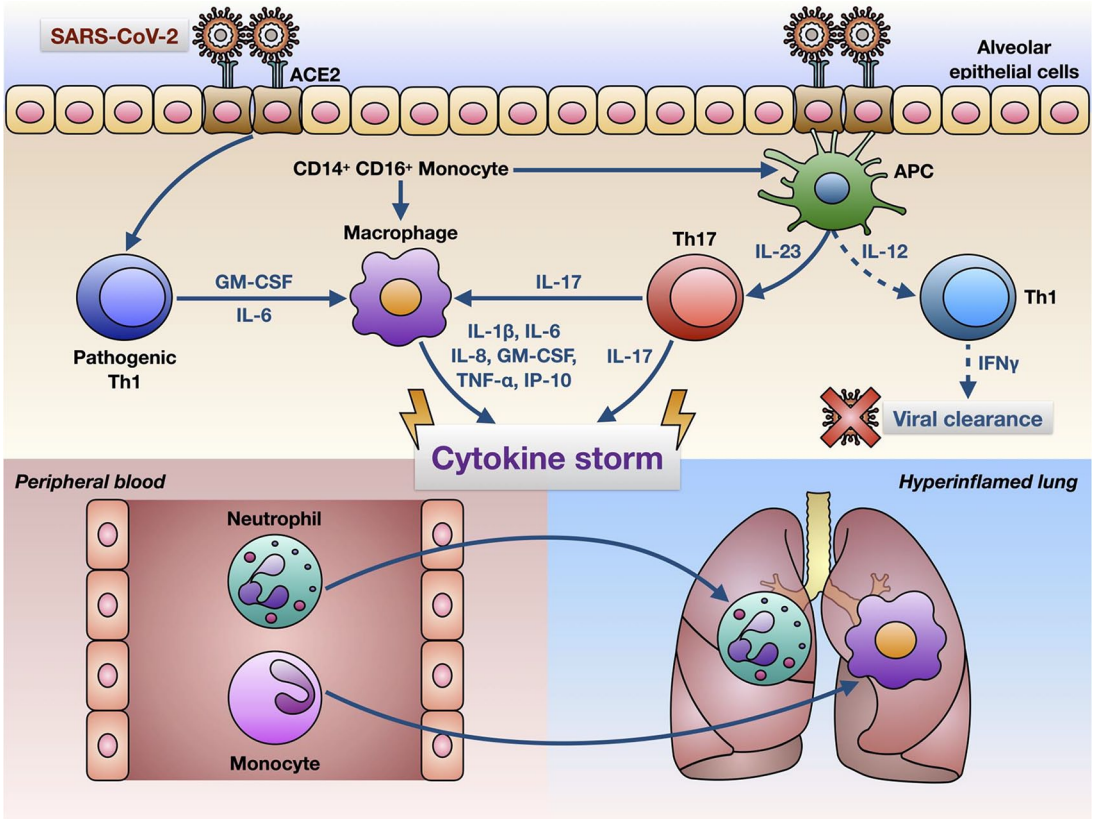

Figure 1. Hypothetical mechanisms underlying the cytokine storm induced by SARS-CoV-2 in infected lungs. SARS-CoV-2 enters target cells (e.g. alveolar epithelial cells) *via* interaction with the ACE2 receptor, thus triggering a complex immune response characterised by activation of pathogenic Th1 cells, $CD14^+$ $CD16^+$ monocytes, alveolar macrophages and Th17 lymphocytes. These cells release high amounts of cytokines and chemokines, responsible for the cytokine storm sustaining a 'hyperinflammatory' environment featured by lung infiltration with neutrophils and macrophages. In critically ill COVID-19 patients with ARDS, the Th1-driven immune adaptive response leading to viral clearance appears to be defective (dashed lines).
ACE2, angiotensin-converting enzyme 2; APC, antigen presenting cells; ARDS, acute respiratory distress syndrome; COVID-19; coronavirus disease 2019; GM-CSF, granulocyte macrophage-colony stimulating factor; IFN, interferon; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; Th, T helper.

release a broad array of proinflammatory cytokines and chemokines (cytokine storm), including interleukins-1β (IL-1β), 2 (IL-2), 6 (IL-6), 7 (IL-7), 8 (IL-8), 17 (IL-17), 18 (IL-18), 33 (IL-33), GM-CSF, interferon-γ-inducible protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), tumour necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) (Figure 1).[1,16]

IL-6 plays a central role in the COVID-19 cytokine storm

One of the most important cytokines produced as a consequence of SARS-CoV-2-induced TLR-7 signalling is IL-6, a pleiotropic proinflammatory mediator that promotes the proliferation of myeloid progenitor cells and the growth and activation of leukocytes, as well as induces pyrexia and the synthesis of acute phase proteins such as C reactive protein (CRP) (Figure 2).[25] IL-6 plays a central role in immune responses by stimulating the differentiation of T follicular helper cells (Tfh) and contributing, together with TGF-β, to development of Th17 cells (Figure 2).[5,24] Through activation of the SOCS-3 (suppressor of cytokine signalling-3) pathway, IL-6 can also suppress phosphorylation of signal transducer and activator of transcription-4 (STAT-4), thus impairing the activity of $CD8^+$ cytotoxic and natural killer T cells.[5,25] Furthermore, *via* up-regulation of IL-4 and down-regulation of IFN-γ, IL-6 inhibits antiviral Th1 cell commitment and favours Th2 cell differentiation.[5] Elevated levels of IL-6 are associated

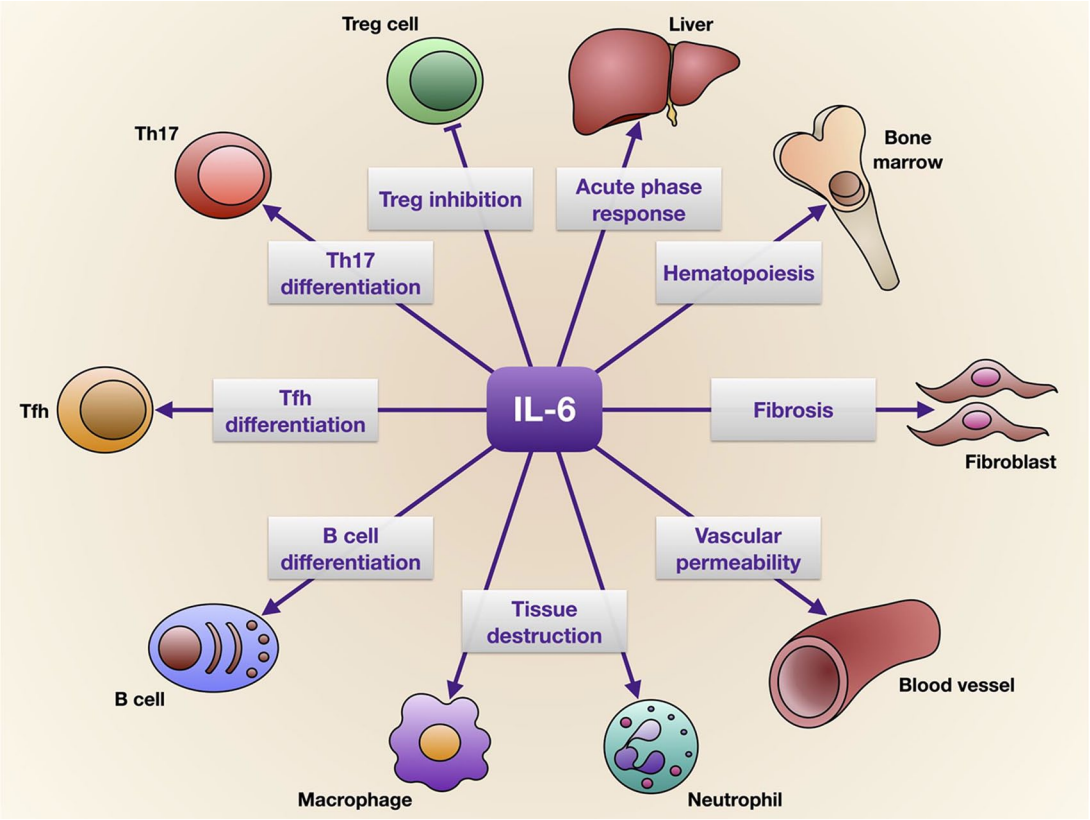

Figure 2. Pleiotropic effects of IL-6, which exerts its biological actions on several cells, tissues and organs. IL-6, interleukin-6; Th, T helper cells; Tfh, T follicular helper cells; Treg, regulatory T cells.

with severe lung injury.[26] IL-6 can suppress the functions of T lymphocytes, dendritic cells and macrophages aimed to eliminate coronaviruses, thereby dampening the ability of the immune system to clear such infections.[27] Therefore, IL-6 overproduction can probably be induced by some viruses such as SARS-CoV-2, with the aim of escaping immune surveillance.

Role of other cytokines in COVID-19 cytokine storm

Active IL-1β and IL-18 originate from their inactive precursors *via* a cleavage catalysed by caspase-1, a proteolytic enzyme operating within the context of the multiprotein intracellular inflammasome complex,[28] highly susceptible to activation induced by viral molecules. IL-1β and TNF-α, mostly generated by activated macrophages, are present in high concentrations in bronchoalveolar lavage fluid (BALF) from patients with ARDS and stimulate neutrophil functions.[29–31] TNF-α also causes the apoptotic death of lung epithelial and endothelial cells.[32]

High IL-8 BALF concentrations have been also detected in subjects with ARDS.[31] IL-8 is a powerful chemoattractant and activator of neutrophils, whose apoptosis is inhibited by this chemokine. Thus, upon release from monocytes/macrophages and alveolar epithelial cells, IL-8 plays a key role in stimulating neutrophil survival and recruitment to the lungs.[31] IL-8 synthesis is effectively stimulated by IL-17A and IL-17F secreted by IL-6-dependent Th17 cells, which are likely involved in triggering the cytokine storm associated with lung neutrophilic infiltration.[24] Indeed, high numbers of Th17 lymphocytes can be found in peripheral blood of patients with severe SARS-CoV-2 infection.[33]

With regard to inflammatory cell influx into SARS-CoV-2-infected lungs, a key pathologic function is also exerted by GM-CSF, which mediates relevant intercellular communications between pathogenic Th1 cells and $CD14^+$ $CD16^+$ monocytes (Figure 1).[18] High numbers of $CD14^+$ $CD16^+$ monocytes are detectable in COVID-19 patients with severe involvement of lungs, where these cells actively participate in

induction and amplification of tissue infiltration by macrophages.[18]

Another proinflammatory mediator potentially involved in the cytokine/chemokine storm characterising severe SARS-CoV-2 infection is the chemokine IP-10. In fact, it has been previously shown that IP-10 is up-regulated in bronchiolar and alveolar epithelial cells, as well as in T cells and monocytes/macrophages infiltrating the lungs of subjects with SARS.[30] IP-10 exerts a strong chemotactic action on T lymphocytes, monocytes and natural killer cells.[30] Moreover, high blood levels of IP-10 were detected in patients died of SARS.[34] It is thus very likely that IP-10 significantly contributes to the recruitment of monocytes/macrophages into the lungs of SARS patients. Virus-induced production of IP-10 could also be responsible for a fast mobilisation, followed by a subsequent apoptosis of T cells[30]; this mechanism might be implicated in the impairment of T lymphocyte response against SARS-CoV-2.

Consequences of cytokine storm

Taken together, the above considerations suggest that, in critically ill COVID-19 patients, cytokine storm and cytokine dysregulation lead to remarkable pathological consequences. Indeed, the cytokine storm elicits immunological changes that can potentially weaken the immune response aimed to clear SARS-CoV-2 infection. T lymphocyte-dependent protective responses against SARS-CoV-2, mediated by both $CD4^+$ and $CD8^+$ T cells, may potentially fail because of the overproduction of IL-6 and TNF-α. In fact, these cytokines can inhibit T cell proliferation and activation, thereby contributing to the development of lymphopenia in severely injured SARS-CoV-2 infected patients.[16,18] Consistent with such a speculation, it has been reported that high levels of both IL-6 and TNF-α coexist with relatively low counts of $CD4^+$ and $CD8^+$ T cells.[21] It has been also hypothesised that a suppression of functionally exhausted Th1 lymphocytes might be concomitant with an immunological shift towards Th2-driven responses.[1,16] All the above immunological changes likely occur more often in the elderly, because of a negative impact of aging on the protective efficiency afforded by the adaptive immune network against new viral infections.[6]

Cytokine/chemokine-mediated injury of lung endothelial and epithelial cells may impair the integrity of blood/air barrier, thereby promoting vascular permeability as well as alveolar oedema, infiltration by inflammatory cells (i.e. neutrophils and macrophages) and hypoxia.[32] In addition, the presence within the cytokine storm context of fibrogenic factors such as TGF-β could favour tissue remodelling and lung fibrosis,[30] thus further compromising gas exchange.

Diagnosis of cytokine storm

In clinical setting, there is an urgent need to detect the laboratory parameters which can be useful to diagnose cytokine storm. A recent meta-analysis of 21 studies globally including 3377 patients and 33 laboratory biomarkers suggests that elevated serum levels of IL-6 and ferritin, paralleled by high numbers of white blood cells and associated with low lymphocyte and platelet counts, could provide a valuable diagnostic platform for critical COVID-19 illness.[35] Such data are partially consistent with those of a very recent explorative study carried out on 127 hospitalised COVID-19 patients, which showed that, when compared with the group of less severe subjects, more severe patients were characterised by high blood levels of IL-6, fibrinogen, sialic acid, CRP and neutrophils.[36] In particular, neutrophil-to-lymphocyte ratio (NLR) resulted to be significantly higher in severely ill patients,[36] thus suggesting that the decreased lymphocyte count might be indicative of the existing impairment of the immune system.

Therapeutic implications for SARS-CoV-2-induced cytokine storm

Several drugs, currently approved for treatment of various diseases and acting on different molecular targets, are potentially useful to lessen the strength of the cytokine storm triggered by SARS-CoV-2.[37] However, their utilisation in COVID-19 patients is mostly empirical, because of lack of published controlled trials showing a reliable profile of efficacy and safety. Such drugs include IL-6 receptor antagonists, IL-1 receptor antagonists, JAK/STAT (Janus kinases/signal transducers and activators of transcription) inhibitors, corticosteroids, hydroxychloroquine and azithromycin.

IL-6 receptor antagonists

An effective inhibitor of IL-6 pathogenic action within the context of SARS-CoV-2-induced

cytokine storm appears to be tocilizumab, a recombinant humanised monoclonal antibody targeting the IL-6 receptor, currently utilised for treatment of rheumatoid arthritis.[38,39] A retrospective Chinese study, performed in 21 severely ill COVID-19 patients, showed that tocilizumab safely lowered fever and CRP, as well as improving hypoxemia and computed tomography (CT) scan lung lesions.[40] On the basis of these positive results, a randomised controlled trial has been approved in China with the aim of testing tocilizumab in subjects with elevated IL-6 levels and interstitial pneumonia (ChiCTR2000029765).[3] Tocilizumab is also undergoing clinical investigation in Italy (Trial TOCIVID-19–NCT04317092). Current Chinese and Italian guidelines recommend the use of tocilizumab for treatment of COVID-19 infection.[16] In particular, Italian guidelines suggest that tocilizumab should be utilised in patients with interstitial pneumonia and severe respiratory failure, characterised by high blood levels of IL-6 or CRP/D-dimer/fibrinogen/ferritin.[16] A further phase III clinical trial has been approved by the United States Food and Drug Administration (FDA) to evaluate tocilizumab in hospitalised COVID-19 patients suffering from severe pneumonia [ClinicalTrials.gov identifier: NCT04320615]. However, the use of tocilizumab raises some concerns. Indeed, it is possible that the high viral load that drives the cytokine storm would be unsuppressed by the use of tocilizumab. Furthermore, although tocilizumab seems to be usually quite safe and well tolerated, it has been reported that the infusion of this drug can occasionally be associated with the occurrence of liver damage, thrombocytopenia, leukopenia, serious infections, gastrointestinal perforations, hypertension, skin reactions and anaphylaxis.[41] Another IL-6 receptor antagonist is sarilumab, already licensed for treatment of rheumatoid arthritis and currently undergoing a phase II/III clinical trial enrolling severely ill hospitalised COVID-19 patients [ClinicalTrials.gov identifier: NCT04315298].[42]

IL-1 receptor antagonist

Anakinra is a recombinant antagonist of human IL-1 receptor that appears to be capable of improving the survival of septic patients with macrophage activation syndrome (MAS).[43] In particular, in 43 septic patients with MAS and concomitant disseminated intravascular coagulation, hepatobiliary dysfunction, cytopenias and hyperferritinemia, when compared with placebo, anakinra treatment significantly improved the 28-day survival rate (anakinra: 65.4%; placebo: 35.3%).[43]

JAK/STAT inhibitors

Inhibitors of JAK/STAT (signal transducers and activators of transcription) signalling pathways such as baricitinib, a drug that is currently utilised to treat rheumatoid arthritis, can be potentially useful for treatment of cytokine storm. Indeed, by targeting the JAK/STAT signal transduction system, baricitinib interferes with the functions of adaptor-associated protein kinase 1 (AKK1) and cyclin G-associated kinase (GAK), which are implicated in viral endocytosis.[44] Fedratinib is a specific JAK2 inhibitor able to reduce IL-17 expression, as well as to repress GM-CSF biological actions.[24] Therefore, this drug could contribute to attenuate the cytokine storm associated with severe SARS-CoV-2 infection. Another JAK inhibitor is ruxolitinib, a drug that is currently utilised for treatment of myelofibrosis. Ruxolitinib has been shown to induce relevant clinical benefits in some COVID-19 patients treated in Southern Italy (unpublished observations). However, further studies are needed to corroborate and validate such positive preliminary data.

Corticosteroids

The use of systemic corticosteroids for treatment of COVID-19-associated cytokine storm could be of some value. In fact, by modulating cytokine production, these drugs might repress hyperinflammation associated with COVID-19-related ARDS.[45] Some interesting observations suggest that in community-acquired pneumonia corticosteroids could increase the rate of therapeutic success, and also decrease the number of hospitalisation days and the time occurring to reach clinical stability.[46] However, it has been reported that early use of hydrocortisone in subjects with MERS could delay viral clearance.[47] Moreover, utilisation of methylprednisolone in SARS-CoV-2 infected patients with advanced ARDS and progressive disease appears to ameliorate respiratory symptoms and CT abnormalities, but does not seem to prolong overall survival.[48,49] Nevertheless, because of the lack of control arms, such conclusions based on observational studies should be considered with extreme caution.

Hydroxychloroquine and azithromycin

Chloroquine, and especially its less toxic derivative hydroxychloroquine, could block SARS-CoV-2 entry inside target cells by interfering with glycosylation of ACE2 receptors.[50] This drug also acts by suppressing TLR7 signalling and by inhibiting endosomal acidification, essential for viral replication.[5] Moreover, hydroxychloroquine prevents endolysosomal fusion. The therapeutic action of hydroxychloroquine can be potentiated by azithromycin, capable of reducing the pro-inflammatory activity of IL-6 and TNF-α.[51,52]

Conclusion

The dramatic outbreak of SARS-CoV-2 infection is currently associated with an ongoing progress in the knowledge of underlying pathogenic mechanisms, which is shedding partial light on the immunophenotypic traits characterising infected patients more susceptible to the development of heavy lung damage caused by cytokine storm. Indeed, an impairment in anti-viral immune response and the concurrent aberrant hyperinflammatory reaction can facilitate, especially in elderly people with comorbid conditions, the occurrence of the most severe forms of COVID-19-related illness. A better understanding of cytokine storm pathobiology is also making it possible to explore the therapeutic efficacy of IL-6 receptor antagonists and JAK/STAT inhibitors, which, however, require to be carefully evaluated by definitely needed randomised controlled trials.

Author contribution(s)

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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