The role of IL-6 and IL-6 blockade in COVID-19

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces a dysregulated hyperinflammatory response.

Areas covered: Authors review evidence on IL-6 and IL-6 blockade in coronavirus disease 2019 (COVID-19) and discuss the pathophysiological and prognostic roles of this cytokine and the clinical impact of pharmacological blockade of IL-6. The material includes original articles and reviews published from March 2020 to March 2021 and searched on PubMed, medRxiv, and bioRxiv.

Expert opinion: IL-6 is one of the most prominent pro-inflammatory cytokines. Increased levels are recorded in COVID-19 patients, especially those with severe-to-critical disease. Evidence is accumulating on the relevance of IL-6 as a prognostic marker in COVID-19. Since IL-6 is a druggable target for several inflammatory diseases, pharmacological blockers of the IL-6 signaling pathway were repurposed to blunt the abnormal SARS-CoV-2-induced cytokine release. Data are limited to few randomized controlled trials that reported encouraging, though not conclusive, results, indicating the usefulness of IL-6 blockade early in the course of the disease in patients with hyperinflammation and no or limited organ damage. Further research is warranted to explore the role of IL-6 in different COVID-19 phenotypes and identify subgroups of patients who may mostly benefit from IL-6 pathway inhibition.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents with a mild form of upper respiratory infection or no symptoms at all in the majority of individuals [1]. A subgroup of patients, however, may progress to severe and critical disease experiencing acute hypoxic respiratory failure, acute respiratory distress syndrome (ARDS), multi-organ failure and not infrequently death [2]. SARS-CoV-2 induces a dysregulated hyperinflammatory response in later stages as the virus was found to infect monocytes, macrophages, and dendritic cells (DCs) that increase the secretion of pro-inflammatory cytokines including interleukin-6 (IL-6) [2].

IL-6 is one of the most important pro-inflammatory cytokines [3] and was discovered in late ‘80s [4]. After its molecular cloning, IL-6 was found to be identical to other proteins with different functions, indicating its pleiotropic nature. The IL-6/IL-6 receptor (IL-6 R) axis is known to be involved in the pathophysiology of many diseases and its inhibition has been already proven to be beneficial in rheumatoid arthritis, Castleman disease, and the cytokine release syndrome following chimeric antigen receptor (CAR) T cell therapy, among others [5].

In COVID-19, IL-6 is believed to drive multi-organ injury, the most severe form of the illness [6,7] (Figure 1). To this end, IL-6 blockade was postulated to help reducing the inflammatory burden of COVID-19 in the setting of a cytokine storm [8] and improve the clinical status of patients [9,10]. In this narrative review, we summarize basic concepts about IL-6 biology and currently approved therapeutic indications for IL-6 blockade. Then, we discuss in detail the relevance of IL-6 in the pathophysiology of COVID-19 along with its prognostic implications. The safety and efficacy of IL-6 pathway inhibition in COVID-19 is also extensively covered. Finally, we provide future perspectives about the role of IL-6 based on contemporary evidence.

2. Search criteria

The material for this review includes original articles and reviews published over the past year (from March 2020 to March 2021) and searched on PubMed through the following search terms or their combination: ‘IL-6’, ‘SARS-CoV-2’, ‘COVID-19’, ‘cytokine storm’, ‘cytokine release syndrome’, ‘IL-6 blockade’, ‘IL-6 inhibitors’, ‘tocilizumab’, ‘sarilumab’, ‘siltuximab’, and ‘outcomes’. We considered only English language papers. Additional articles identified from the reference list of the searched articles and from medRxiv and bioRxiv (free online
3. Overview of IL-6 biology signaling pathway

IL-6 is a pleiotropic cytokine that not only regulates the immune system and the inflammatory response but also affects hematopoiesis, metabolism, organ development, and cancer growth and maintenance [11]. IL-6 mediates several distinct pathophysiological processes depending on activated signaling pathways and cytopathotypes [12].

IL-6 binds to the membrane-bound IL-6 R that consists of two functional chains, IL-6 Ra and a non-ligand-binding chain glycoprotein of 130 kDa (gp130), the latter being responsible for signal transduction. IL-6 first binds to the IL-6 R then to gp130 forming a trimer (Figure 2A). Two close trimers homodimerize to form an hexameric signaling complex which mediates gene activation and a wide range of biologic activities involving the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)3, and src homology 2 (SH2) containing protein tyrosine phosphatase-2 (SHP2)/Grb2-associated

Figure 1. SARS-CoV-2 induces a deregulated, hyperinflammatory response mediating organ injury. After binding its receptor - angiotensin-converting enzyme 2 (ACE2) - SARS-CoV-2 enters type II pneumocytes and replicates. Following viral invasion, macrophages, neutrophils, and dendritic cells activate to capture SARS-CoV-2. Damaged cells release pathogen-associated molecular patterns (PAMPs) stimulating further recruitment of immune cells, that in turn release a large amount of pro-inflammatory cytokines, including IL-6. These mediators are responsible for the increased permeability of alveolar vessels and further immune cell recruitment to the site of infection, thus sustaining the positive, hyperinflammatory loop. Because of lung vessel permeability, SARS-CoV-2 can spread to other organs rich in ACE2, such as kidney, intestine, and pancreas, explaining clinical manifestations other than respiratory ones.

Legend. ACE2: angiotensin-converting enzyme 2. APC: antigen presenting cell. IFN: interferon. IL: interleukin. NET: neutrophil extracellular trap. PAMP: pathogen-associated molecular pattern. ROS: reactive oxygen species. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TNF: tumor necrosis factor. Reproduced with permission from Gubernatorova et al., ‘IL-6: Relevance for immunopathology of SARS-CoV-2’ [7].
binder (Gab)/mitogen-activated protein kinase (MAPK) and phosphoinositide-3 kinase (PI3K) intracellular signaling pathways [13–15]. Only few cells, such as macrophages, neutrophils, cluster of differentiation (CD)4⁺ T cells, podocytes, and hepatocytes express IL-6 R on their cell surface and can activate this classic signaling pathway [13].

A soluble form of the IL-6 R (sIL-6 R) is also found in body fluids, such as blood and urine. sIL-6 R derives from
the cleavage of IL-6 R by the membrane-bound a disintegrin and metalloprotease 17 (ADAM17) [16]. An alternative mechanism for sIL-6 R generation is mediated by the translation of a differentially spliced IL-6 R messenger ribonucleic acid (mRNA) lacking the transmembrane and cytosolic domains [17]. sIL-6 R binds IL-6 with the same affinity of the membrane receptor, and the IL-6/sIL-6 R complex activates gp130, that is ubiquitously expressed on cell surface, and can induce signaling also on those cells lacking the membrane-bound IL-6 R [18]. This kind of gp130 activation, termed IL-6 trans-signaling pathway, allows modulation of a broad spectrum of target cells [19,20] (Figure 2A).

In human plasma, a soluble form of gp130 (sgp130) can be retrieved and derives primarily from alternative splicing rather than from proteolysis. sgp130 can interact with the IL-6/sIL-6 R complex and such a property makes sgp130 a very inhibitor of IL-6 trans-signaling pathway without affecting classical signaling [21].

These complex regulatory mechanisms enable IL-6 to play a wide plethora of biological activities mainly depending on distinct effector cells and activated signaling cascades. In particular, the classic signaling pathway appears to impact vital and regulatory functions of cells presenting IL-6 R on their surface (e.g., neutrophils, naïve T cells, and hepatocytes), while the trans-signaling pathway is a driver of dysregulated inflammatory responses potentially affecting all cells (Figure 2B).

By focusing on the effects on inflammation and immunity, IL-6 can promote the differentiation of naïve CD4+ T cells (linking innate and acquired immunity), the T helper (Th)17 differentiation, the T follicular helper cell differentiation, IL-21 production (regulating immunoglobulin synthesis), the differentiation of CD8+ T cells into cytotoxic T cells, the differentiation of activated B cells into antibody-secreting plasma cells, macrophage activation, bone marrow megakaryocyte maturation, and inhibition of transforming growth factor (TGF)-β-induced regulatory T cell differentiation [5,22]. IL-6 can also induce vascular endothelial growth factor production, that increases vascular permeability and angiogenesis and stimulates receptor activator of nuclear factor κ beta (RANKL) to differentiate and activate osteoclasts [22].

The activation of IL-6 pathways is responsible to induce hepatocytes to synthesize and release acute-phase proteins (C-reactive protein [CRP], serum amyloid A, fibrinogen, haptoglobin, and α1-antichymotrypsin) and reduce the synthesis of fibrinectin, albumin, and transferrin [23]. IL-6 is also important for the induction of hepcidin during inflammation, that finally leads to the typical hypoferremia of inflammation [24].

In light of its pleiotropic effects, IL-6 signaling pathway has become an attractive druggable target to blunt the inflammatory signaling that contributes to the pathogenesis of several diseases.

4. Current indications for IL-6 blockade

Several clinical trials explored the potential benefits of IL-6 inhibition on systemic symptoms of inflammatory diseases. The first IL-6 pathway inhibitor was the humanized monoclonal antibody tocilizumab, which binds to both sIL-6 R and membrane IL-6 R, thus preventing the formation of the complex with IL-6 and signal transmission [25]. Sarilumab is another human monoclonal antibody targeting both sIL-6 R and membrane IL-6 R [26]. The positive results of clinical trials testing IL-6 R blockers for the treatment of inflammatory diseases led to the production of several other antibodies directly targeting IL-6 (i.e., siltuximab and sirukumab, olokizumab, and clazakizumab).

The use of IL-6 inhibitors has been extensively evaluated in a number of randomized clinical trials (RCTs) in patients with rheumatoid arthritis [27] (Table 1). Tocilizumab was shown to improve signs and symptoms of the disease, radiological progression, and patients’ quality of life [28–42]. It is approved for rheumatoid arthritis treatment in combination with methotrexate, and is the drug of choice as monotherapy in patients unable to be treated with methotrexate [43]. Tocilizumab is currently used to treat systemic-onset juvenile idiopathic arthritis [44,45] and adult-onset Still’s disease [46], whereas no benefit has been found in the treatment of ankylosing spondylitis [47]. Conflicting results came from studies on systemic lupus erythematosus, with tocilizumab that seemed promising in a phase I study [48]. Tocilizumab is the first drug approved for giant cell arteritis other than glucocorticoids [49,50]. In Japan, this drug was approved also for Takayasu arteritis, although the primary efficacy endpoint was not met in the phase III study [51]. Potential benefits in lung function decline were reported in patients with systemic sclerosis treated with tocilizumab [52]. More recently, based on retrospective analyses of pooled data from prospective clinical trials of CAR T cell therapies, tocilizumab was approved for the treatment of severe or life-threatening CAR T-cell-induced cytokine release syndrome [53].

Sarilumab also obtained the approval for the treatment of rheumatoid arthritis based on clinical trials showing its favorable efficacy and safety [59–61].

The effectiveness of sirukumab was proven in patients with active rheumatoid arthritis refractory to disease-modifying anti-rheumatic drugs (DMARDs) [62,63], despite not being superior to adalimumab [64]. RCTs with sirukumab failed to prove the efficacy of IL-6 inhibition in systemic lupus erythematosus [65,66].

Olokizumab also gave promising results for the treatment of patients with moderate-to-severe rheumatoid arthritis for whom methotrexate was inadequate [67–69].

Clazakizumab was shown to be effective for the treatment of musculoskeletal manifestations in patients with psoriatic arthritis, but no improvements in skin disease were observed [70].

Both siltuximab and tocilizumab are approved for the treatment of multicentric Castleman disease [71,72] and are indicated for unresectable unicentric Castleman disease with inflammatory symptoms [73], although limited data exist for the unicentric form [74].
General information about the current use of IL-6 inhibitors can be found in Table 1.

5. Pathophysiological role of IL-6 in COVID-19-related dysregulated cytokine response

According to the clinical–therapeutic staging of COVID-19 [75], IL-6 plays a pivotal role in the third stage, that is characterized by an abnormal systemic hyperinflammatory response. The dysregulated cytokine release is clinically responsible for severe COVID-19, whose main marker is abnormal IL-6 levels [76,77]. IL-6 is produced by a subset of highly inflammatory macrophages [78], but not by alveolar macrophages, which are low or absent in the bronchoalveolar fluid of severely ill patients [79]. Of interest, while IL-6 absence at early phases of a viral infection was shown to depress T follicular helper cell maturation thus reducing antiviral response [80], COVID-19 patients admitted to the intensive care unit (ICU) show a negative correlation between IL-6 and other cytokines, as well as CD4+ and CD8+ T cells [81]. This indicates that aberrant IL-6 production has a negative impact on adaptive immunity.

An exaggerated hyperinflammatory response was reported by early studies in China in patients with COVID-19, which described markedly increased levels of several inflammatory mediators, including – but not limited to – IL-6, IL-1β, IL-18, IL-8, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF) [82–85].

| Disease | IL-6 blocker | Main results |
|---------|--------------|--------------|
| Rheumatoid arthritis | Tocilizumab | Improvement in signs and symptoms in patients with active RA without increase in incidence of AEs [28–34], even on long-term follow-up [35,36]; improvement in signs and symptoms in patients with active RA who had inadequate response to TNF antagonists [37] and DMARDs [38]; reduction in radiographic disease progression [39]; superiority of tocilizumab compared with methotrexate in sign and symptom reduction in patients with active RA [40]; superiority of tocilizumab compared with adalimumab in sign and symptom reduction in patients with severe RA [41,42] |
| Systemic juvenile idiopathic arthritis | Tocilizumab | CR and normalization of inflammatory biomarkers in open-label studies in children with active sJIA [54,55] and in pivotal studies; greater improvement of signs and symptoms in patients with active sJIA compared with placebo [44,45] and catch-up growth |
| Adult-onset Still’s disease | Tocilizumab (in Japan) | Improvement in CR in patients with AOSD refractory to glucocorticoids without reaching the statistically significant difference compared with placebo; decrease in glucocorticoid dose [46] |
| Giant cell arteritis | Tocilizumab | Better CR in patients with a new diagnosis or recurrence of giant cell arteritis [49] |
| Takayasu arteritis | Tocilizumab (in Japan) | Improvement in time to relapse in tocilizumab group compared to placebo in PPS analysis but not in the ITT populations [51] |
| Cytokine release syndrome | Tocilizumab | CR in CRS caused by CAR T-cell therapies (retrospective analysis of pooled data from prospective CTs of CAR T-cell therapies) [53] |
| Castleman disease | Tocilizumab | Improvement in inflammatory symptoms and reduction in steroid dose in patients with multicentric Castleman disease without increase in incidence of AEs [71] |
| Systemic lupus erythematosus | Siltuximab | Improvement in inflammatory symptoms and in patients with multicentric Castleman disease without increase in incidence of AEs [72] |

Positive initial results (not yet approved)

| Disease | IL-6 blocker | Main results |
|---------|--------------|--------------|
| Crohn’s disease | Tocilizumab | Improvement in CR rate in patients with active Crohn’s disease treated for 12 weeks without increase in incidence of AEs [56] |
| Systemic sclerosis | Tocilizumab | Reduction in forced vitality capacity decline in tocilizumab group compared with placebo group; no difference in skin thickening reduction [52] |
| Rheumatoid arthritis | Sirukumab | Improvement in symptom, structural damage progression and quality of life in patients with active RA refractory to DMARDs [62,63] |
| Psoriatic arthritis | Olokizumab | Greater CR compared with placebo in patients with moderate-to-severe RA [67,68] |
| Clazakizumab | Improvement in musculoskeletal manifestations compared with placebo, but not in skin disease [70] |

Negative preliminary results

| Disease | IL-6 blocker | Main results |
|---------|--------------|--------------|
| Multiple myeloma | Siltuximab | No improvement in CR rate or long-term outcomes with the addition of siltuximab to bortezomib-melphalan-prednisone regimen in patients with a new diagnosis of multiple myeloma [57] |
| Ankylosing spondylitis | Tocilizumab | No benefit in the treatment of patients with ankylosing spondylitis [47] |
| Sarilumab | No benefit in the treatment of patients with ankylosing spondylitis [58] |
| Systemic lupus erythematosus | Sirukumab | No benefit in patients with active SLE [65] and in those with lupus nephritis [66] |

AE: adverse event; AOSD: adult-onset Still’s disease; CR: clinical response; DMARD: disease-modifying anti-rheumatic drug; ITT: intention-to-treat; PPS: per-protocol set; RA: rheumatoid arthritis; sJIA: systemic juvenile idiopathic arthritis; SLE: systemic lupus erythematosus; TNF: tumor necrosis factor
It appears now clear that patients with higher levels of inflammatory mediators experience worse outcomes during SARS-CoV-2 infection [86,87]. In particular, COVID-19 patients progressing to ARDS showed increased concentrations of IL-6, IL-1β, and tumor necrosis factor (TNF-α) [82]. This abnormal increase in cytokine levels, described as a cytokine storm, is responsible for an exaggerated activation of the immune system that, in turn, promotes further production of cytokines and chemokines. Importantly, dysregulated inflammation seems to be associated with abnormalities in the coagulation cascade, finally leading to immunothrombotic processes [88], which are also responsible for organ damage.

SARS-CoV-2 infects preferentially type II pneumocytes and alveolar macrophages within the lungs [89,90]. Recently, Patra et al. showed that the SARS-CoV-2 spike protein can trigger an angiotensin II type 1 (AT1) receptor-mediated signaling cascade, finally increasing IL-6 release, which is down-regulated by the AT1 receptor antagonist candesartan [91]. In the lungs, the virus replicates and alters the lung epithelial layer thus entering underlying tissues, where immune cells – namely neutrophils, macrophages, and dendritic cells (DCs) – capture the pathogen [7]. In lung samples of patients who died because of COVID-19-related ARDS, SARS-CoV-2 was found to trigger the activation of the NACHT, LRR, and PYD domains-containing protein 3 (NLRC3) inflammasome in monocytes [92,93,155] leading to the production and release of IL-1β, which is upstream of IL-6.

Injured pneumocytes can release danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), that trigger the activation of the lung epithelium and resident immune cells [90,94]. Activation of neutrophils and macrophages, antigen presentation by DCs, and local SARS-CoV-2 replication lead to increased production of inflammatory cytokines, especially IL-6, IL-1β, and TNF-α, finally contributing to organ damage, especially the lungs, as this uncontrolled inflammatory response is able to self-propagate [95]. Indeed, a correlation between IL-6 and viral load was described, with the latter being associated with ARDS severity and lung damage [96]. Finally, during infections, increased vessel permeability allows immune cell infiltration and viral spread, followed by the release of inflammatory mediators, such as IL-6, that exacerbate the hyperinflammatory environment [97].

Lymphopenia is commonly observed among COVID-19 patients and correlates with disease severity [98]. Injured spleen and lymph nodes and increased IL-6 levels, by inducing lymphocyte apoptosis, are likely to play a role in the development of lymphopenia [98,99]. IL-6 was also shown to affect the lymphoid function through a marked reduction in human leukocyte antigen D related (HLA-DR) expression coupled by an important depletion of CD4+ lymphocytes, CD19+ lymphocytes, and natural killer (NK) cells [100].

IL-6 is also involved in the COVID-19-associated coagulopathy [101] as it is known to interfere with the coagulation cascade through the generation of tissue factor and thrombin [102,103], to stimulate platelet activity, and induce endothelial dysfunction [104]. With this regard, tocilizumab seems to improve the hypercoagulable state in COVID-19 patients, irrespective of prophylactic or therapeutic dose of anticoagulant therapy, and was associated with a parallel improvement in respiratory function [105]. Recently, Canzano et al. provided evidence that COVID-19 coagulopathy may be supported by diffuse cell activation mediated by tissue factor produced by platelets, granulocytes, and microvesicles on the common background of endothelial dysfunction, with all of these events strongly sustained by increased levels of IL-6. Indeed, IL-6 blockade with tocilizumab and antiplatelet drugs (aspirin or P2Y12 inhibitors) were found beneficial in blunting these effects [106].

6. IL-6 as a prognostic marker in COVID-19

Coronaviruses including SARS-CoV-2 have the ability to induce, in a subgroup of infected subjects, an excessive and dysregulated immune response which appears to be crucial in the progression of disease [8,76].

Initial evidence from postmortem analyses of fatal COVID-19 cases due to refractory ARDS revealed diffuse pulmonary interstitial mononuclear inflammatory infiltrates, predominantly lymphocytic and perivascular, associated with overactivation of cytotoxic T cells and high concentrations of cytotoxic mediators, whose local or systemic biological activity is believed to substantially contribute to organ damage and to the development of severe forms of COVID-19 [107,108]. Similarly, a large number of early reports from China describing the immunological profile of severe COVID-19 patients demonstrated the hyperactivation of the humoral immune pathways [86,96,109–112]. As evidence is mounting, it became clear that, among a large number of biomarkers examined, IL-6 plays an essential role in COVID-19, being mechanistically implicated in disease pathogenesis and clinically associated with prognosis [6,7]. Notably, IL-6 has been already proven to be a valuable biomarker in a wide spectrum of diseases including pneumonia of other etiologies, and is frequently employed in clinical practice worldwide [23,113,114].

Salient observations by Chen et al. showed that increased baseline IL-6 was closely associated with vital signs and the detection of serum SARS-CoV-2 RNAemia, which appears to be a distinctive feature of critical disease [96]. Furthermore, critically ill patients displayed almost 10-fold higher IL-6 levels compared with severe patients, and all fatal cases exhibited extremely elevated IL-6 values [96]. In the early phase of the pandemic, these and other similar findings [86,96,109,111,112,115] contributed to link the immunological features of severe-to-critical COVID-19 to those of cytokine storm syndromes [8,116]. Increased baseline IL-6 was also positively associated with other inflammatory biomarkers, such as CRP, lactate dehydrogenase (LDH), ferritin, and D-dimer, and chest computed tomography (CT) findings [112]. Likewise, lower IL-6 levels were found in patients recovering from COVID-19 with improved findings on chest CT scan, whereas IL-6 was further increased during disease re-exacerbation [112]. Furthermore, analysis of bronchoalveolar lavage of patients with COVID-19 revealed that IL-6 was significantly higher in ICU patients compared with non-ICU patients, thus providing further evidence of the local (pulmonary), besides systemic (serum), involvement of IL-6 [94].
A large number of meta-analyses confirmed the relevance of IL-6 as a prognostic marker in COVID-19 [117–121]. With regard to disease severity, meta-analyses found that, despite considerable heterogeneity, systemic levels of IL-6 were significantly higher in severe COVID-19 patients compared with non-severe cases [117–121]. IL-6 appeared to be able to discriminate disease severity across the clinical spectrum of COVID-19, as patients with progressively worse disease displayed proportional increases in IL-6 levels [117]. A meta-analysis from Zhu et al. found that IL-6 concentration of patients with mild COVID-19 was on average 24.49 pg/mL, lower than that of severely ill patients, whose IL-6 was on average 30.66 pg/mL, which was lower than that of critically ill patients [117]. Compared with non-complicated COVID-19, mean IL-6 concentrations were almost 3-fold higher in complicated cases, including severe-to-critical patients and those developing ARDS or requiring ICU admission, with the results being consistent when restricting the analysis to patients requiring or not ICU admission [119]. Furthermore, a study by Herold et al. found that IL-6 was highly predictive of the need for invasive ventilation, with IL-6 cutoff >35 pg/mL at hospital admission, and maximal values >80 pg/mL [77]. Of note, elevated IL-6 levels in the course of disease predicted respiratory failure significantly earlier than CRP did (23.2 vs 15.7 hours) [77].

Besides reflecting disease severity, IL-6 levels also appear to predict fatality risk from COVID-19. A number of studies have consistently reported that, compared with survivors, non-survivors displayed markedly increased IL-6 values, with mean between-group differences ranging from 41.32 to 59.88 pg/mL [117,118,121]. Interestingly, Laguna-Goya et al. developed an IL-6-based mortality risk model for hospitalized patients with COVID-19 including, besides IL-6, peripheral blood oxygen saturation to fraction of inspired oxygen ratio (SpO\textsubscript{2}/FiO\textsubscript{2}), neutrophil-to-lymphocyte ratio, LDH, and age, that showed high accuracy for the prediction of fatality [122].

Data herein reported demonstrate that circulating levels of IL-6 are closely associated with clinical outcomes and survival rates in patients with COVID-19. Monitoring of IL-6 dynamic changes, together with other biomarkers such as CRP and D-dimer, may therefore be advisable, since it anticipates the clinical evolution of disease serving as an early warning indicator and allowing physicians to adequately manage patients who might benefit from early treatment escalation (i.e. anti-cytokine strategies). It is, however, worth considering that, when employing IL-6 levels to make clinical decisions, these should be interpreted with caution as they might be influenced by multiple confounding factors, such as age, comorbidities, treatments, and genetic polymorphisms [123].

Elevated concentrations of inflammatory cytokines, including IL-6, observed in severe-to-critical COVID-19 have spurred comparisons with other syndromes of critical illness that are associated with increased cytokine concentrations [8]. A study by Leisman et al. found that elevations of IL-6 are markedly lower in patients with COVID-19 than those reported in patients with ARDS unrelated to COVID-19, sepsis and CAR T cell therapy-induced cytokine release syndrome, thus highlighting the need for a deeper understanding of the pathobiology of COVID-19 [124].

Given the central role of IL-6 in the pathogenesis of COVID-19 and its role as a prognostic biomarker, IL-6 signaling pathway inhibition was identified as an attractive therapeutic strategy in COVID-19 and has been evaluated for the treatment of COVID-19 by a large number of studies.

7. IL-6 signaling pathway blockade in COVID-19

Recently, IL-6 signaling pathway blockade with IL-6 inhibitors tocilizumab, sarilumab, and siltuximab has been investigated for the treatment of hyperinflammation associated with COVID-19 (Table 2 and Figure 3).

7.1. Tocilizumab

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody targeting the soluble and membrane-bound IL-6 R [125].

Shortly after SARS-CoV-2 outbreak, based on evidence showing a key involvement of IL-6 in the pathobiology of COVID-19, physicians in China initiated the off-label use of tocilizumab in seek for an urgent effective treatment. After an initial 21-patient retrospective cohort study by Xu et al. reporting on the potential clinical benefits of intravenous tocilizumab (4–8 mg/kg) in severe-to-critical COVID-19 patients [126], tocilizumab has been extensively administered either on a compassionate-use basis or within research settings worldwide. In the earlier phases of the pandemic, tocilizumab has become the preferred anti-inflammatory therapy for patients with rapidly progressing acute respiratory failure and hyperinflammation. A large number of observational studies in patients at different stages of COVID-19 described the potential usefulness of both intravenous and subcutaneous tocilizumab in quenching the hyperinflammatory response, as shown by a rapid and sustained reduction of inflammatory biomarkers, including CRP, ferritin and D-dimer, which was paralleled by an improvement in gas exchanges, as shown by significant increases in pressure of arterial oxygen to fractional inspired oxygen concentration (PaO\textsubscript{2}/FiO\textsubscript{2}) [127–132]. Despite considerable heterogeneity in tocilizumab administration (route, dose, timing), lack of standardized background therapeutic schemes, and limitations due to the observational nature of these studies, changes in inflammation- and oxygenation-related parameters observed after tocilizumab treatment seemed to be associated with a trend toward reduced risk for clinical worsening, assessed by decreased need for mechanical ventilation or death [127–132]. In contrast, other observational studies reported limited efficacy of tocilizumab in COVID-19 [133,134]. Interestingly, a prospective cohort study with 138 patients by Masía et al. found tocilizumab did not impair the viral specific antibody response, and the observed delayed viral clearance was likely associated with initially higher viral loads, thus supporting the safety of IL-6 blockade [135]. Cumulatively, meta-analyses of observational studies with low-certainty evidence found that the addition of tocilizumab to standard-of-care was associated with a lower risk of ICU admission, use of ventilation, and mortality across all degrees of COVID-19 severity, without significantly
Table 2. Main results from completed randomized controlled trials evaluating IL-6 inhibitors for the treatment of COVID-19.

| Study                  | Study design and location | Study population                                                                 | IL-6 inhibitor          | Efficacy outcomes                                                                 | Safety outcomes                                                                 |
|------------------------|---------------------------|-----------------------------------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| RCT-TZC-COVID-19       | Open-label randomized trial; Italy, 24 centers | Patients with acute respiratory failure with PaO2/FIO2 between 200 and 300 mmHg at enrollment and inflammatory phenotype. Patients requiring NIV, IMV and/or ICU admission were excluded. | IV TCZ (8 mg/kg, up to 800 mg) within 8 hours from randomization, followed by a second dose after 12 hours | • Clinical worsening by day 14: 17/60 (28.3%) in the T茨茨 arm vs. 17/63 (27.0%) in the SOC arm (RR 1.05; 95% CI 0.59–1.86).<br>• IMV by day 30: 6/60 (10.0%) in the T茨茨 arm vs. 5/63 (7.9%) in the SOC arm.<br>• Death by day 30: 2/60 (3.3%) in the T茨茨 arm vs. 1/63 (1.6%) in the SOC arm. | • AEs: 14/60 (23.3%) in the T茨茨 arm vs. 7/63 (11.1%) in the SOC arm.<br>• SAEs: 1/60 in the T茨茨 arm (upper GI tract bleeding) vs. 2/63 in the SOC arm (severe infections) |
| Salvarani et al. (NCT04346355) [139] | BACC Bay Tocilizumab Trial | Patients with a hyperinflammatory state and at least two of the following signs: body temperature >38 °C, pulmonary infiltrates, or need for supplemental oxygen to maintain an oxygen saturation >92%. Patients receiving more than 10 L/min of supplemental oxygen were excluded. | Single dose of IV TCZ (8 mg/kg) | • MV or death by day 28: 17/161 (10.6%) in the T茨茨 arm vs. 10/81 (12.5%) in the placebo arm (HR 0.83, 95% CI 0.38–1.81, P = 0.64).<br>• Clinical worsening by day 28: 31/161 (19.3%) in the T茨茨 arm vs. 14/81 (17.4%) in the placebo arm (HR 1.11; 95% CI 0.59–2.10, P = 0.73).<br>• MV by day 28: 11/161 (6.8%) in the T茨茨 arm vs. 8/81 (10.0%) in the placebo arm (HR 0.65, 95% CI 0.26–1.62).<br>• Death by day 28: 9/161 (5.6%) in the T茨茨 arm vs. 3/81 (3.8%) in the placebo arm (HR 1.52, 95% CI 0.4–5.61). | • ALT elevation, grade ≥3: 8/161 (5.0%) in the tocilizumab arm vs. 4/82 (4.9%) in the placebo arm (P = 0.99).<br>• AST elevation, grade ≥3: 6/161 (3.7%) in the T茨茨 arm vs. 3/82 (3.7%) in the placebo arm (P = 0.99).<br>• Neutropenia, grade ≥3: 22/161 (13.7%) in the T茨茨 arm vs. 1/82 (1.2%) in the placebo arm (P = 0.002).<br>• Infections, grade ≥3: 13/161 (8.1%) in the T茨茨 arm vs. 14/82 (17.1%) in the placebo arm (P = 0.03) |
| Stone et al. (NCT043566937) [140] | Randomized, double-blind, placebo-controlled trial; Global (Canada, Denmark, Italy, The Netherlands, Spain, UK, USA), 67 centers | Patients with blood oxygen saturation ≤93% or PaO2/FIO2 < 300 mmHg. Patients were excluded when death was considered imminent and inevitable within 24 hours. | Single dose of IV TCZ (8 mg/kg, up to 800 mg), followed by a possible second dose after 8–24 hours if sustained fever or worsened ordinal scale clinical status | • Clinical status based on 7-category ordinal scale at day 28 (median): 1.0 in the T茨茨 arm vs. 2.0 in the placebo arm (OR 1.19, 95% CI 0.99 to 2.05).<br>• Ventilator-free days by day 28 (median): 22.0 in the T茨茨 arm vs. 16.5 in the placebo arm (difference 5.5, 95% CI −2.8 to 13.0, P = 0.32).<br>• Death by day 28: 58/294 (19.7%) in the T茨茨 arm vs. 28/144 (19.4%) in the placebo arm (WD, 0.3, 95% CI −7.6 to 8.2, P = 0.94). | • AEs: 228/295 (77.3%) in the T茨茨 arm vs. 116/143 (81.1%) in the placebo arm.<br>• SAEs: 103/295 (34.9%) in the T茨茨 arm vs. 55/143 (38.5%) in the placebo arm.<br>• Liver events: 52/295 (1.7%) in the T茨茨 arm vs. 3/143 (2.1%) in the placebo arm.<br>• Serious infections: 62/295 (21.0%) in the T茨茨 arm vs. 37/143 (25.9%) in the placebo arm |
| Bosco et al. (NCT04320615) [141] | Cohort-embedded, investigator-initiated, open-label, bayesian randomized controlled trial; France, 9 centers | Patients with confirmed COVID-19 pneumonia requiring at least 3 L/min of supplemental oxygen, but without HFO, NIV, IMV or ICU admission | IV TCZ (8 mg/kg, up to 800 mg) on day 1, followed by a possible second fixed dose of 400 mg on day 3 if oxygen requirement was not decreased by more than 50% | • MV or death by day 14: 17/63 in the T茨茨 arm vs. 27/67 in the SOC arm (HR 0.58, 95% CI 0.26–1.23).<br>• Death by day 28: 7/63 in the T茨茨 arm vs. 8/67 in the SOC arm | • AEs: 28/63 (44%) in the T茨茨 arm vs. 36/67 (54%) in the SOC arm.<br>• SAEs: 20/63 (32%) in the T茨茨 arm vs. 29/67 (43%) in the SOC arm (P = 0.21).<br>• Liver events: 4/63 in the T茨茨 arm vs. 4/67 in the SOC arm (P = 0.003).<br>• Neutropenia: 4/63 in the T茨茨 arm vs. 0/67 in the SOC arm (P = 0.003).<br>• Bacterial sepsis: 2/63 in the T茨茨 arm vs. 11/67 in the SOC arm (P = 0.003) |

(Continued)
increasing the risk for infections or adverse events, such as elevation of transaminases or neutropenia [136,137].

These promising data accumulating from observational studies prompted the initiation of a large number of RCTs testing tocilizumab for COVID-19. Nevertheless, the initial controlled experiences with tocilizumab failed, showing that tocilizumab was marginally or not effective for the treatment of severe-to-critical COVID-19 [138]. In the small open-label RCT-TCZ-COVID-19 trial involving 126 hospitalized patients with COVID-19 and PaO2/FiO2 between 200 and 300 mmHg, tocilizumab (8 mg/kg up to a maximum of 800 mg intravenous infusion, followed by a second infusion after 12 hours) had no benefit on disease progression compared with standard-of-care, leading to the premature interruption of the study [139]. In the BACC Bay Tocilizumab trial that enrolled 243 non-mechanically ventilated patients with hyperinflammation, a single 8 mg/kg tocilizumab dose, while showing a good safety profile, was not effective in preventing intubation or death [140]. In the larger double-blind COVACTA trial that randomized 452 patients to receive tocilizumab (8 mg/kg) or...
placebo, a shorter time to hospital discharge (20 vs. 28 days, P = 0.037) and a reduced duration of the ICU stay (9.8 vs. 15.5 days, P = 0.045) were found in patients treated with tocilizumab compared with placebo [141]. In the cohort-embedded, open-label, Bayesian randomized CORIMUNO-19 trial of hospitalized patients with COVID-19 pneumonia requiring oxygen support but not admitted to ICU, tocilizumab (single intravenous infusion of 8 mg/kg, with a possible second dose, if clinically indicated) significantly reduced the risk of mechanical ventilation or death by day 14, however no difference on day-28 mortality was found [142]. A similar signal for efficacy of tocilizumab in COVID-19 was observed in the randomized, double-blind, placebo-controlled EMPACTA trial that included a group of 389 racial and ethnic minority patients who were not receiving mechanical ventilation [143]. In this study, treatment with tocilizumab (one or two 8 mg/kg intravenous doses) was safe and significantly reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, while it showed no effect on survival compared with placebo [143].

Recently, very encouraging results from two large RCTs have been released [144,145]. In the multifactorial, adaptive platform REMAP-CAP trial, critically ill subjects with COVID-19 requiring oxygen support in ICU were randomized to receive either tocilizumab (dose of 8 mg/kg, 353 patients), sarilumab (dose of 400 mg, 48 patients) or standard-of-care (402 patients). Administration of one of the IL-6 inhibitors markedly improved outcomes including days free from organ support (10, 11 and 0 days for tocilizumab, sarilumab and control, respectively) and in-hospital mortality (28%, 22.2% and 35.8% for tocilizumab, sarilumab and control, respectively) [144]. The open-label, platform RECOVERY trial randomized 4,116 patients receiving supplemental oxygen (82%), noninvasive respiratory support (41%), or invasive mechanical ventilation (14%), and evidence of hyperinflammation (CRP $\geq$75 mg/L) to receive tocilizumab (400–800 mg intravenously, with a second possible dose 12–24 hours later, if clinically indicated) plus standard-of-care, or standard-of-care alone [145]. Overall, 29% vs. 33% of subjects died within 28 days (rate ratio 0.86; 95% confidence interval [CI] 0.77–0.96; p = 0.007), with benefits observed regardless of the level of respiratory support [145]. Of note, in patients receiving concomitant systemic glucocorticoid treatment at randomization (82%), a clear effect on mortality was observed, showing that the benefits of tocilizumab were additional to those of glucocorticoids [145]. Furthermore, patients treated with tocilizumab were more likely to be discharged alive from hospital by day 28 (54% vs 47%; rate ratio 1.22; 95% CI 1–12–1.34; p < 0.0001) [145]. In summary, tocilizumab in patients with severe COVID-19 pneumonia was shown to be safe and reduce progression to mechanical ventilation [143,145] and death [145], although not all studies showed the same benefits.

### 7.2. Sarilumab

Sarilumab is a fully human monoclonal antibody that antagonizes both soluble and membrane-bound IL-6 R [125]. With the exhaustion of tocilizumab supplies, sarilumab was repurposed for the treatment of COVID-19 due to its shared mechanism of action with tocilizumab. In parallel with encouraging data with tocilizumab, initial uncontrolled experiences with sarilumab also yielded promising expectations leading to the initiation of multiple phase II/III RCTs (NCT04324073, NCT04386239, NCT04357808, NCT04322773). For instance, in a small prospective single-center case-series from Italy, seven out of eight patients treated with sarilumab, administered as three single intravenous infusions of 400, 200 and 200 mg respectively at 24, 48 and 96 hours after hospital admission, showed an improvement in inflammatory biomarkers, pulmonary ultrasound score and oxygenation, and patients were discharged within 7 days [146]. Moreover, sarilumab (400 mg on day one, with a possible second infusion in case of unchanged or worsened clinical status) showed a favorable efficacy and safety profile among 53 severe-to-critical patients, leading to resolution of COVID-19 pneumonia in 83% of cases (89.7% and 64.3% for patients treated in medical wards and ICU, respectively) [147]. However, in an open-label cohort study of 28 COVID-19 patients not on invasive mechanical ventilation, a single sarilumab infusion of 400 mg did not significantly improve survival when compared with matched controls, despite being associated with faster recovery (10 vs. 24 days) in a subset of patients with limited lung consolidations at baseline [148]. Likewise, in a larger cohort of 255 patients, treatment with either tocilizumab (400 mg) or sarilumab (200 mg) was associated with better clinical outcomes in patients with lower oxygen requirements, although the study lacked a control group and the mortality of patients treated with the IL-6 R inhibitor was comparable with the overall mortality of the local New York city area [149].

Controlled evidence with sarilumab is currently limited to disappointing results from two RCTs. In the first trial, sarilumab administration was not associated with a statistically significant difference in clinical outcomes, although there was a beneficial effect in clinical improvement and mortality among mechanically ventilated patients. This, however, was counterbalanced by a detrimental effect in non-mechanically ventilated patients, leading to the early interruption of the study and the cancellation of the originally planned extension trial testing higher sarilumab dosage (800 mg) [150]. In a separate trial enrolling 420 critical COVID-19 patients, sarilumab treatment (200 or 400 mg) was associated with a positive signal, but it did not reach statistical significance [151]. In REMAP-CAP trial, sarilumab was found to increase organ support-free days compared with control (11, interquartile range [IQR] 0–16 vs. 0, IQR –1 – 15), with a median adjusted odds ratio (OR) of 1.76 (95% credible interval [CrI] 1.17–2.91). Sarilumab also reduced in-hospital mortality compared with controls (22.2% vs. 35.8%), with an adjusted OR of 2.01 (95% CrI 1.18–4.71) [152]. In summary, sarilumab showed a favorable effect on survival in patients with severe COVID-19 pneumonia in one RCT, while it was neutral in two other trials.

### 7.3. Siltuximab

Siltuximab is a chimeric monoclonal antibody that prevents IL-6 from binding to its receptors and inhibits the biological activity of IL-6 [125]. Siltuximab has been recently
deemed of interest for the treatment of COVID-19. Although there are no published studies supporting the use of siltuximab for COVID-19, findings from a non-peer reviewed report from Italy suggest that siltuximab, administered intravenously at a dose of 11 mg/kg to 30 patients requiring noninvasive mechanical ventilation, induced a rapid and sustained decline in CRP, was well-tolerated, and associated with a significantly lower mortality rate compared to standard-of-care alone [153]. A multicenter Belgian RCT (NCT04330638) comparing siltuximab (11 mg/kg intravenously, alone or in combination with the IL-1 blocker anakinra) to other cytokine inhibitors (anakinra and tocilizumab, alone or in combination) has just completed the enrollment, with results being expected soon [154].

8. Conclusion

Following the initial emphasis on the role of IL-6 and the cytokine storm in driving the clinical manifestations of SARS-CoV-2 infection, it is now apparent that IL-6 is an important mediator in COVID-19 but should be mostly regarded as a marker of disease severity. Indeed, increased levels of IL-6 in COVID-19 were found to have a negative prognostic role toward adverse outcomes, especially need for mechanical ventilation and death. In light of this, IL-6 pathway blockade was evaluated in several RCTs with overall encouraging results. In particular, in two RCTs – the EMPACTA and RECOVERY trials – testing IL-6 R blockers, tocilizumab and sarilumab reduced the risk for mechanical ventilation and death [143,145]. It is, however, important to carefully interpret results from these trials in order to adequately select the best candidates. In particular, patients with early signs of hyperinflammation and minimal or no evidence of organ damage may mostly benefit from IL-6 pathway inhibition, whereas IL-6 pathway inhibition later in the course of disease (e.g. when ARDS or multi-organ dysfunction is present) may result in limited clinical benefit. Adequately designed and powered studies are urgently needed to identify specific subgroups of COVID-19 patients who may mostly benefit from cytokine inhibition, as well as the optimal timing of IL-6 R inhibitor administration and early predictors of treatment success or failure. It is now recognized that SARS-CoV-2 may activate a wealth of redundant, inflammatory pathways including the IL-1 pathway [8,92,93,155], that could provide a kind of escape mechanism from IL-6 blockade. Therefore, whether the co-administration of other immunomodulatory agents (e.g., glucocorticoids, IL-1 blockers, Janus kinase 2 [JAK2] inhibitors) synergistically maximize the benefits of IL-6 pathway blockade still remains to be determined. Finally, whether the inhibition of the abnormal cytokine response would be beneficial in reducing long-term effects in patients recovering from severe forms of COVID-19 is not known and certainly deserves further investigation. Based on available evidence, IL-6 blockade should be carefully considered for those patients presenting with an early hyperinflammatory phenotype and acute respiratory failure but without substantial organ damage.

9. Expert opinion

The role of IL-6 in COVID-19 was largely investigated over the past months, coming to the conclusion that it is an important mediator of the clinical manifestations of patients progressing toward a moderate-to-severe COVID-19 [5,82,156,157]. With this in mind, early during the SARS-

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**Figure 3.** IL-6 blockade in clinical practice. IL-6 is known to take part to inflammatory events, immune responses, and acute-phase reactions in a wealth of inflammatory diseases. The binding of IL-6 to IL-6 R and/or sIL-6 R is responsible for the activation of the intracellular classical and trans-signaling pathways. IL-6 has a role in the pathogenesis of rheumatoid arthritis, Castleman disease, systemic juvenile idiopathic arthritis, giant cell arteritis, Takayasu arteritis, and cytokine release syndrome following CAR T cell therapy, just to cite the most important ones. IL-6 blockade has become a druggable target consisting in the pharmacological inhibition of IL-6 directly or through its binding to IL-6 R and/or sIL-6 R. Currently available drugs targeting either IL-6 or its receptor are presented in the picture. The picture is adapted from Rose-John S, ‘Interleukin-6 signalling in health and disease’ [11], that is an open access article distributed under the terms of the Creative Commons Attribution License.
CoV-2 pandemic, IL-6 blockade using monoclonal antibodies was investigated with potential benefits described in several observational or cohort studies [105,127,131,158–161]. However, some contrasting data from RCTs with the IL-6 R blocker tocilizumab have raised questions on the real usefulness of these drugs and posed some questions about the real role played by IL-6 in severe COVID-19 [10,139,140,142,143,162,163]. So, why is it difficult to draw definitive conclusions based on currently available data?

In the middle of a pandemic rapidly spreading all around the world, a class of drugs, namely the IL-6 pathway blockers, was repurposed in the attempt to reduce as much as possible poor outcomes, such as progression to mechanical ventilation and death. However, previously described trials incorporate considerable heterogeneity (e.g., different severity of respiratory failure and hyperinflammation, different background therapies). In addition, it should be considered that there are still some difficulties in defining the optimal therapeutic window for administering immunomodulatory drugs. It is generally recognized that cytokine inhibitors, when administered too early in the course of disease, may harm, however late administration may result in blunted clinical benefits, since organ damage has already occurred and several cytokines may be involved in the pathogenesis at that stage. These caveats are worth being further investigated by designing trials addressing these clinical knowledge gaps.

Another point to consider is the adequacy of IL-6 as the sole marker to be considered when choosing to administer an IL-6 blocker. Accumulating evidence is likely to suggest that IL-6 alone should not be considered, but other more specific mediators, such as PaO2, CRP, ferritin, and D-dimer, might also be helpful in identifying patients progressing toward severe-to-critical COVID-19 who can benefit more from these therapies [164]. While initially similarities between the cytokine storm occurring in patients receiving CAR T cell therapy and that occurring in patients with SARS-CoV-2 infection were postulated [165], the impact of the presumed cytokine storm in COVID-19 has been now downsized to an abnormal or eventually dysregulated cytokine response when compared with other conditions leading to elevated IL-6 levels [124,166,167,168]. With this regard, Kox et al. compared cytokine levels, including IL-6, of patients with COVID-19-related ARDS with those of patients with septic shock and out-of-hospital cardiac arrest and found that IL-6 was lower in COVID-19 than in other conditions [167], probably depicting a globally lower disease severity in spite of a severe pulmonary injury. In a recent systematic review and meta-analysis [124], levels of IL-6 in severe-to-critical COVID-19 were compared with those in ARDS, CAR T cell therapy-associated cytokine release syndrome, and sepsis and were found to be extremely lower of at least 30 to nearly 100 times (mean 36.7 pg/mL, 95% CI 21.6–62.3 pg/mL vs. 3,110.5 [632.3–15,302.9] pg/mL in CAR T cell therapy-induced cytokine release syndrome vs. 1,558.2 [525.8–4,617.6] pg/mL in hyperinflammatory ARDS vs. 983.6 [550.1–1,758.4] pg/mL in sepsis) (Figure 4).

**Figure 4. IL-6 levels in different inflammatory conditions.** When compared to other inflammatory diseases, such as CAR T cell therapy-induced cytokine release syndrome, sepsis, or hyperinflammatory ARDS, levels of IL-6 in COVID-19 appear to be extremely low. Markers indicate point estimates and error bars indicate 95% confidence intervals. Reproduced with permission from Leisman DE, ‘Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes’ [124].
In sum, individuals with hyperinflammation (marked by increased levels of IL-6, CRP, ferritin, and D-dimer) should benefit from IL-6 pathway blockers early in the disease course, when no organ injury (marked by lactate dehydrogenase) still exists. Whether cytokine blockade upstream of IL-6 (i.e. IL-1 blockade) is beneficial remains yet to be proven, as no RCTs directly comparing IL-6 and IL-1 inhibitors are currently available. As the activation of NLRP3 signaling pathway was demonstrated in COVID-19 [92,93,155], IL-1 blockade might be theoretically superior than IL-6 blockade alone, probably because the upstream inhibition of IL-1 may lead to a downstream reduction of IL-6 and, possibly, other inflammatory cytokines [168]. Collectively, these aspects need to be urgently addressed in order to unravel the actual role of different anti-cytokine treatments in COVID-19 and maximize clinical benefits of such therapeutic strategies.

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