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Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)?

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ABSTRACT

The emergent outbreak of coronavirus disease 2019 (COVID-19) has caused a global pandemic. Acute respiratory distress syndrome (ARDS) and multiorgan dysfunction are among the leading causes of death in critically ill patients with COVID-19. The elevated inflammatory cytokines suggest that a cytokine storm, also known as cytokine release syndrome (CRS), may play a major role in the pathology of COVID-19. However, the efficacy of corticosteroids, commonly utilized antiinflammatory agents, to treat COVID-19-induced CRS is controversial. There is an urgent need for novel therapies to treat COVID-19-induced CRS. Here, we discuss the pathogenesis of severe acute respiratory syndrome (SARS)-induced CRS, compare the CRS in COVID-19 with that in SARS and Middle East respiratory syndrome (MERS), and summarize the existing therapies for CRS. We propose to utilize interleukin-6 (IL-6) blockade to manage COVID-19-induced CRS and discuss several factors that should be taken into consideration for its clinical application.

The newly emerging coronavirus disease 2019 (COVID-19), first reported in Wuhan, China, has swept across 202 countries with stunning mortality. The World Health Organization (WHO) has declared this deadly outbreak a pandemic, with tremendous ramifications impacting every life. By March 27, 2020, the number of deaths had climbed to 23,495 among 512,701 confirmed cases in WHO reports [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel beta-coronavirus, has been identified as the pathogen for COVID-19 [2]. This strain has been the third most lethal pathogenic human coronavirus, following severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses in 2003 and 2012, respectively. SARS-CoV-2 targets the lung and likely other organs as well, leading to multiorgan damage by binding to the angiotensin-converting enzyme 2 (ACE2) receptor [2], a cell surface protein highly expressed in the lung, heart and kidney [3].

Clinical data from Wuhan, China, showed that approximately 17.7–32.0% of patients require intensive care unit (ICU)-level care, with approximately 9.5–12.0 days from symptom onset to multiorgan dysfunctions, namely, acute respiratory distress syndrome (ARDS) (67%), acute kidney injury (29%), acute cardiac injury (23%), and liver dysfunction (29%) [4–6]. The mortality of critically ill patients is as high as 49.0–61.5% [4,5]. Evidence suggests that CRS might play a major role in severe COVID-19. Inflammatory cytokines and chemokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), induced protein 10 (IP10) and monocyte chemoattractant protein-1 (MCP-1) were significantly elevated in COVID-19 patients, and some were more commonly seen in severe patients than in nonsevere patients (Table 1). In COVID-19 patients with elevated inflammatory cytokines, postmortem pathology has revealed tissue necrosis and interstitial macrophage and monocyte infiltrations in the lung, heart and gastrointestinal mucosa [7,8]. Moreover, severe lymphopenia with hyperactivated proinflammatory T cells [8] and decreased regulatory T cells [9] is commonly seen in critically ill patients, suggesting dysregulated immune responses.

CRS refers to an uncontrolled and overwhelming release of proinflammatory mediators by an overly activated immune system [10]. CRS is a common immunopathogenesis underlying many pathological processes, such as ARDS, sepsis, graft-versus-host disease (GvHD), macrophage activation syndrome (MAS) induced by rheumatic diseases, and primary and secondary hemophagocytic lymphohistiocytosis (HLH)

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Table 1
The levels of cytokines in patients with COVID-19, SARS and MERS versus those in normal controls.

Cytokines	COVID-19	SARS	MERS
IL-6	↑ in some [36,58] or in severe cases [6,34,54]	↑	Unknown but ↑ in severe than in mild cases
IL-2	↑	↑ or NS	NS
IL-1β	↑	NS	Unknown
IL-8	↑	↑	Unknown
IL-17	↑	Unknown	↑
IFN-γ	↑	NS	↑
TNF-α	↑	NS	↑
IP10	↑	↑	Unknown but ↑ in severe than in mild cases
MCP-1	↑	↑ or NS	Unknown
IL-10	↑	NS or ↑ in convalescent cases	↑
IL-4	↑	NS or ↓ in convalescent cases	NS
Ref	[6,33,34,36,54,58]	[28,59–61]	[62,63]

Up or down arrows indicate higher or lower levels versus normal controls, respectively. Abbreviations: NS; no significant change versus normal controls, IL: interleukin, IFN-γ: interferon γ, IP: induced protein, MCP: monocyte chemoattractant protein, TNF-α: tumor necrosis factor α.

[11]. Recently, CRS has also been reported to be a complication of immunotherapies, such as chimeric antigen receptor (CAR) T cell therapies [12]. Previous experience with SARS and MERS has also revealed florid CRS in critically ill patients (Table 1). Studies have shown that ARDS occurs in some SARS patients despite a diminishing viral load, suggesting that an exuberant host immune response rather than viral virulence is possibly responsible for tissue pathologies. Therefore, antiviral therapy alone may be inadequate [13]. Corticosteroids, one of the most widely utilized anti-inflammatory agents, are still commonly prescribed in treating COVID-19 patients (72.2% in the ICU setting) [14]. However, as outlined in the Chinese guidelines of COVID-19 [15], physicians need to be cautious of steroid use due to its nebulous benefits in the setting of viral respiratory infection. Several studies even reported inferior outcomes of SARS patients treated with corticosteroids [16]. Another concern of corticosteroids is their short- and long-term adverse effects. More than half of SARS patients treated with corticosteroids suffer from joint pain and bone marrow abnormalities [17]. Other therapies aiming to dampen excessive serum inflammatory mediators, such as plasmapheresis or continuous renal replacement therapy (CRRT), either require specific equipment or lack documented efficacy [18]. Thus, there is still an unmet need for the treatment of COVID-19-induced CRS [19]. In the past decade, immunotherapy has made great strides in managing CRS of various etiologies, including autoimmunity, malignancy and CAR T cell therapies (Table 2). We propose herein that attenuating the detrimental host immune response by immunomodulators may be a beneficial addition to antiviral therapy.

A better understanding of the pathogenesis underlying CRS may facilitate the design of novel immunotherapies. The immunologic mechanism of CRS induced by coronaviruses is not fully elucidated, and existing data are largely derived from SARS coronavirus (SARS-CoV), a close counterpart of SARS-CoV-2. It is believed that delayed kinetics of virus clearance are the trigger. The delayed type I interferon (IFN) response plays a pivotal role in the process of SARS. In the initial phase, SARS-CoV evades pattern recognition receptors (PRRs) and antagonizes the type I IFN response by inducing double-membrane vesicles that lack PRRs, mRNA capping and proteins that inhibit PRR downstream cascades [20,21]. The dampened type I IFN in airway and alveolar epithelial cells results in rapid viral replication. Plasmacytoid dendritic cells (pDCs) and macrophages are exceptions, with a full response to SARS-CoV, launching a delayed but robust type I IFN response and releasing other inflammatory cytokines against SARS-CoV [21,22]. Consequently, the activation of type I IFN signaling cascades induces extensive IFN-stimulated gene (ISG) expression and attracts inflammatory monocyte-macrophages (IMMs), neutrophils, dendritic cells and natural killer cells to the lung. This process amplifies the innate response, forming a cytokine-driven vicious cycle [21]. The virus-specific T cell immune response is indispensable for virus clearance, an essential step in protecting mice from lethal SARS-CoV infection [23]. Both regulatory T cells and naïve T cells negatively regulate the activated innate immune responses by cell-cell interactions [24]. Exuberant production of cytokines, such as type I IFN, diminishes T cell responses by inducing T cell apoptosis to aggravate CRS and lymphopenia, as observed in SARS patients [21,25]. The overwhelming proinflammatory cytokines and chemokines cause localized pulmonary injury characterized by diffuse alveolar damage with epithelial and endothelial apoptosis, dysregulated coagulation and pulmonary fibrinolysis. They may also leak into systemic circulation to cause extrapulmonary manifestations and eventually multiple organ dysfunction syndrome [26,27].

Among the excessive cytokines produced by activated macrophages, IL-6 is one of the key cytokines. Elevated IL-6 levels were observed in patients with SARS and were correlated with disease severity (Table 1) [28]. IL-6 activates its downstream Janus kinase (JAK) signal by binding the transmembrane (*cis*-signaling) or soluble form (*trans*-signaling) of the IL-6 receptor (IL-6R) and interacting with membrane-bound gp130 [29]. Excessive IL-6 signaling leads to a myriad of biological effects that contribute to organ damage, such as maturing naïve T cells into effector T cells, inducing vascular endothelial growth factor (VEGF) expression in epithelial cells, increasing vessel permeability [30], and reducing myocardium contractility [31].

The elevated cytokine levels may also be responsible for the lethal complications of COVID-19. As shown in Table 1, patients with COVID-19, SARS or MERS presented distinct cytokine profiles. Patients with COVID-19 presented elevated T helper 2 cytokines (interleukin-4) in addition to T helper 1 cytokines compared to those in patients with SARS or MERS. There are many potential therapies targeting the host immune system that may be effective for COVID-19, such as inflammatory cytokine blockade (IL-6, IL-1, and IFN), stem cell therapy, immune cell depletion, transfusion of convalescent plasma and artificial extracorporeal liver support [32], among which we believe IL-6 blockade is a promising strategy for COVID-induced CRS. We noticed that elevated IL-6 levels were consistently reported in several studies of COVID-19 [33–36] and might serve as a predictive biomarker for disease severity [37]. A large retrospective cohort study found that IL-6 levels were correlated with mortality in patients with COVID-19 [6]. Mechanistically, IL-6 is essential for the generation of T helper 17 (Th17) cells in the dendritic cell-T cell interaction [30]. The excessive IL-6 may explain the overly activated Th17 cells observed in COVID-19 patients, as reported by Xu et al. [8]. Although clinical data of IL-6 blockade in virus infection-related CRS are unavailable, animal studies of SARS-CoV have demonstrated that inhibiting nuclear factor kappa-B (NF-κB), a key transcription factor of IL-6, or infecting animals with SARS-CoV lacking the coronavirus envelope (E) protein, a strong stimulus to NF-κB signaling, increased animal survival, with reduced IL-6 levels [38]. Interestingly, we noticed that the E proteins of SARS-CoV-2

Table 2
Summary of candidate therapies for cytokine release syndrome (CRS) and related diseases.

Therapy	Trigger/associated diseases	Mechanism	Status for hypercytokinemia	Approved by U.S. FDA	Ref
Biologic therapy					
Tocilizumab	MAS, CRS, visceral leishmaniasis-associated HLH, GvHD and sepsis	Human monoclonal anti-IL-6 receptor antibody	● Approval for CAR T cell therapy-associated CRS ● Phase 4 for SARS-CoV-2 (ChiCTR2000029765, NCT04310228, NCT04315480, NCT04317092 …) ● Phase 2 for GvHD (NCT02206035, NCT04070781, NCT03434730, NCT03699631)	Yes	[44,45,64–66]
Siltuximab	CRS	Anti-IL-6 antibody	● Preclinical for CRS	Yes	[67]
Anakinra	MAS, sepsis, HIV/AIDS-associated HLH and CRS	IL-1 receptor antagonist blocking IL-1α and IL-1β	● Phase 1 for MAS (NCT02780583) ● Phase 2 for MAS and sepsis (NCT03332225)	Yes	[68–70]
Canakinumab	MAS	Human monoclonal anti-IL-1β antibody	● Phase 3 for MAS (NCT00889863, NCT00886769, NCT00891046)	Yes	[71,72]
Rilonacep	MAS	Neutralizing IL-1α and IL-1β	● Randomized controlled trial for MAS	Yes	[73]
Rituximab	Epstein-Barr virus-induced HLH, GvHD and MAS	Human monoclonal anti-CD20 antibody to deplete B cells	● Phase 1–2 for GvHD (NCT04235036, NCT01135641, NCT00350545, NCT01001780 …)	Yes	[74–76]
Alemtuzumab	HLH, GvHD	Human monoclonal anti-CD52 antibody	● Phase 2 for HLH (NCT02472054, NCT02385110) ● Phase 1–2 for GvHD (NCT00410657, NCT00495755)	Yes	[77,78]
Ruxolitinib	HLH, GvHD and MAS	Inhibition of JAK/STAT signaling	● Phase 3 for HLH (NCT04120090, NCT03533790) ● Phase 4 for GvHD (ChiCTR1900024408)	Yes	[66,79]
Tofacitinib	GvHD	Selective inhibition of JAK1/JAK3	● Preclinical for GvHD	Yes	[80,81]
Tadekinig alfa	NLRC4-associated MAS	Recombinant human IL-18-binding protein (rhIL-18BP) to tightly bind IL-18	● Phase 3 for NLRC4-associated MAS (NCT03512314, NCT03113760)	No	[82]
Emapalumab	HLH	Anti-IFN γ antibody	● Approval for primary HLH	Yes	[83]
Infliximab	HLH, GvHD and sepsis	Human monoclonal anti-TNFα antibody	● Phase 1–2 for GvHD (NCT00228839, NCT00228839, NCT00201799) ● Phase 4 for GvHD in combination with daclizumab (NCT00574470)	Yes	[84–86]
Etanercept	MAS, GvHD and CRS	Decoy TNF receptor competitively inhibiting TNF	● Phase 2–3 for GvHD (NCT00726375, NCT00141739 NCT00141713, NCT00224874, ChiCTR1900024408)	Yes	[87–89]
Ponatinib	Influenza A	Inhibiting breakpoint cluster region-Abelson (BCR-ABL) kinase to regulate type I IFNs	● Preclinical for cytokine storms in influenza	Yes	[90]
Alternative therapy: corticosteroids, IVIG, chemotherapeutic agents, blood purification, NSAIDs, cell-based therapy and others					
Corticosteroids	Widely used for increased levels of cytokines	Inhibition of HAT and recruitment of HDAC2 activity to the inflammatory gene transcriptional complex to downregulate inflammatory genes	Widely used for cytokine storms ● Phase 4 for SARS-CoV-2 severe pneumonia (NCT04263402, ChiCTR2000029386, ChiCTR2000029656)	Yes	[91]
IVIG	Widely used for increased levels of cytokines	Inhibition of complement activation, blockade of Fc-fragments and Fc receptors and neutralization of cytokines	Widely used for cytokine storms ● Phase 2–3 for SARS-CoV-2 (NCT04261426)	Yes	[92]
Etoposide	Widely used for primary and secondary HLH, but little evidence on HLH induced by influenza or coronavirus	Selective deletion of activated T cells and efficient suppression of inflammatory cytokine production	● Widely used for HLH in combination of corticosteroids and cyclosporine A (HLH2004) ● Preclinical for ARDS	Yes	[79,93,94]
Cyclosporine A	Widely used for primary and secondary HLH, but little evidence on HLH induced by influenza or coronavirus	Inhibition of the translocation into the nucleus of NF-AT to lower the activity of overactivated T cells	● Widely used for HLH in combination with corticosteroids and etoposide (HLH2004)	Yes	[79,93,95]
Cyclophosphamide	MAS	A bioprecursor of a nitrogen mustard alkylation agent to disturb DNA and inhibit cell proliferation	● Phase 3 for HLH in combination with chemotherapies followed by stem cell transplant (NCT00334672) ● Phase 2 for non-Hodgkin's lymphoma with HLH in combination with rituximab and other chemotherapies (NCT01818908)	Yes	[96]

(*continued on next page*)

Table 2 (*continued*)

Therapy	Trigger/associated diseases	Mechanism	Status for hypercytokinemia	Approved by U.S. FDA	Ref
Mycophenolate mofetil	MAS and HLH	Inhibition of inosine monophosphate dehydrogenase to prevent lymphocyte proliferation	● Phase 3 for HLH in combination with other chemotherapies followed by stem cell transplant (NCT00334672)	Yes	[96]
Plasmapheresis	Widely used for increased levels of cytokines	Extracorporeal removal of cytokines, endotoxins, and immunocomplexes	● Randomized single-blind trial for sepsis (NCT01249222)	Yes	[97,98]
Hemofiltration			● Randomized open-label trial for sepsis (NCT03426943)	Yes	[18,98]
Dialysis/hemodialysis			● Randomized open-label trial for sepsis (NCT00537693)	Yes	[99,100]
Hemadsorption			● Trial for sepsis (NCT00559130, NCT02588794 NCT02288975, NCT04226430) ● Randomized open-label trial for transplant-associated hypercytokinemia (NCT03145441, NCT04203004) ● Randomized single-blind trial for CAR T cell-associated CRS (NCT04048434)	Yes	[101]
Aspirin	Acute lung injury and ARDS	Antiplatelet effects to reduce neutrophil recruitment by platelet activation	● Phase 2 for ARDS (NCT01659307)	Yes	[102]
Selective COX-2 inhibitors	Influenza A	Downregulation of COX-2 to decrease proinflammatory cytokine levels	● Phase 3 of celecoxib in combination with oseltamivir for influenza A (NCT02108366)	Yes	[103]
Mesenchymal stem/stromal cells (MSCs)	ARDS, sepsis and GvHD	Alteration of the behavior of both adaptive and innate immune cells	● Approval for GvHD in Canada ● Phase 1–2 for SARS-CoV-2 (NCT04269525, NCT04252118, ChiCTR2000029817, ChiCTR2000029816) ● Phase 1–2 for ARDS (NCT 01775774, NCT 02097641, NCT03818854, NCT 01902082) ● Phase 1–2 for sepsis (NCT03369275, NCT01849237)	Yes	[104,105]
Hematopoietic stem cell transplantation	Primary HLH and refractory HLH	Replacement with a genetically normal bone marrow	● Widely used for familial HLH in children	Yes	[93]
Anti-thymocyte globulin	Primary HLH, MAS and GvHD	Selective ablation of T cells	● Widely used to treat GvHD	Yes	[106]
Statin	Sepsis	Inhibition of hydroxymethylglutaryl-CoA reductase to reduce proinflammatory cytokine levels	● Phase 2–3 for sepsis (NCT00676897, NCT00452608)	Yes	[107]
Chloroquine/hydroxychloroquine	Sepsis and MAS	Inhibition of Toll-like receptors and high mobility group box 1 (HMBG1) to reduce proinflammatory cytokine levels	● Preclinical for sepsis ● Approval for rheumatic diseases and may reduce SLE-induced MAS ● Phase 3–4 for SARS-CoV-2 (NCT04261517, ChiCTR2000029898 …)	Yes	[108,109]
S1P1 agonist (CYM-5442)	Influenza A	S1P1 receptor agonist downregulating inflammatory mediators, possibly by NF-κB signaling	● Preclinical for cytokine storms in influenza A and GvHD	No	[110,111]

Abbreviations: MAS: macrophage activation syndrome, CRS: cytokine release syndrome, HLH: hemophagocytic lymphohistiocytosis, IVIG: intravenous immunoglobulin, CAR: chimeric antigen receptor, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, IL-1: interleukin-1, IL-6: interleukin-6, IL-18: interleukin-18, IFN: interferon. TNF: tumor necrosis factor, JAK/STAT: the Janus kinase/signal transducer and activator of transcription, GvHD: graft-versus-host disease, ARDS: acute respiratory distress syndrome, NSAIDS: nonsteroidal anti-inflammatory drugs, COX-2: cyclo-oxygenase 2; S1P1: sphingosine-1-phosphate receptor 1, NF-κB: nuclear factor kappa-B.

(Ref sequence QHD43418.1) and SARS-CoV (Ref sequence NP_828854.1) share 95% homology. Since the E protein is the determinant of virulence and mediates the host immune reaction to coronavirus [39,40], it is reasonable to speculate that both viruses elicit a similar immune response. Hence, targeting IL-6 may be effective for COVID-induced CRS.

Tocilizumab is a recombinant humanized monoclonal anti-IL-6R antibody. It binds both soluble and membrane-bound IL-6R to inhibit IL-6-mediated *cis*- and *trans*-signaling [41]. Tocilizumab has been approved by the U.S. Food and Drug Administration for the treatment of severe CAR T cell-induced CRS (Table 2) [12]. As mentioned earlier, CRS is the most severe adverse effect induced by CAR T cell therapy, with an incidence of 50–100% [41]. It is believed that binding of the CAR T cell receptor to its antigen induces the activation of bystander cells to release massive a mounts of interferon γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which further activate innate immune cells, including macrophages and endothelial cells, to secrete IL-6 and other inflammatory mediators [42]. IL-6 is a central mediator of toxicity in CRS, and its level correlates with the severity of CAR T cell-induced CRS [12,43]. Clinically, severe cases of CAR-T induced CRS present with fever, hypoxia, acute renal failure, hypotension, and cardiac arrhythmia that often warrants ICU admission [12]. Tocilizumab showed promising efficacy in severe CRS. After one or two doses of tocilizumab, 69% of patients responded within 14 days, for whom fever and hypotension resolved within hours, and vasopressors could be weaned quickly in several days [10,41]. The effect of tocilizumab has also been reported in CRS related to several other conditions, such as sepsis, GvHD and MAS [44–46]. Moreover, tocilizumab is safe for both pediatric and adult patients, as no adverse reactions have been reported in a retrospective analysis of patients with CAR T cell-induced CRS [41]. The most common serious adverse effect is infections in patients with rheumatoid arthritis, in which chronic therapy is maintained for a longer period of time (3.11–3.47/100 person-years with 8 mg/kg tocilizumab every 4 weeks) [47]. Moreover, a possible correlation between tocilizumab and medication-related osteonecrosis of the jaws was reported in patients with osteoporosis [48].

Given the efficacy of tocilizumab in CRS and the pivotal role of IL-6 in COVID-19, we propose to repurpose tocilizumab to treat severe cases of COVID-19. Regarding its clinical use, we suggest taking the following factors into consideration and hope that future clinical trials will be able to address them. 1) Diagnosis criteria. There is currently no consensus in diagnosing CRS in COVID-19. Early diagnosis of CRS in COVID-19 patients and prompt initiation of immunomodulatory treatment may be beneficial, as suggested by the experience in HLH [49]. Prompt screening of COVID-19 patients with Hscore, a diagnostic score for HLH, may help to discriminate patients with CRS [50].2) Disease severity grading system. Experience with immunotherapy-triggered CRS suggests that tocilizumab is indicated only for severe cases, while the risk benefit assessment favors symptomatic management for mild cases [10]. This approach is rationalized by the worry that aggressive antiinflammation therapy may negate the effect of therapeutic biologicals, such as CAR T cells. This principle is not shared in viral infections, such as COVID-19, in which timely intervention in mild or moderate patients may prevent progression. A disease severity grading system may provide an objective tool to assess the most appropriate timing to initiate tocilizumab treatment. Currently, the Chinese guidelines for COVID-19 grade patients into mild, moderate, severe and critical by vital signs, radiographic findings and complications [51]. It is currently unclear which population may benefit the most from the treatment. 3) Combined antiviral treatment. Based on experience with corticosteroids, immunosuppressive agents may delay virus clearance. Combining immunomodulators with antiviral agents may add further benefit. Preliminary results from clinical trials of several antiviral treatments are expected to be available soon (remdesivir [NCT04252664, NCT04257656], favipiravir [ChiCTR2000029600, NCT04310228] and chloroquine [ChiCTR2000029609, NCT04286503]). 4) Secondary infection. Infection is a common adverse effect associated with immunomodulators such as tocilizumab. Critically ill COVID-19 patients are susceptible to secondary infection and may have an increased risk of comorbid chronic infections, such as hepatitis B and tuberculosis [5]. It is unclear to what degree tocilizumab contributes to secondary infection. Hence, the goal of treatment is to prevent or attenuate life-threatening inflammation while minimizing the potential of secondary infection. For this reason, prophylactic antibiotics may be indicated, and bacteriologic and fungal assessments are of great importance. For patients with secondary infection or coexisting chronic infection, the utilization of tocilizumab should be cautious. 5) Cytokine measurement. Cytokine levels may serve as biomarkers for risk stratification and prognosis. A previous cohort study suggested that IL-6 levels were significantly elevated in COVID-19 patients but varied considerably among both ICU and non-ICU patients [34]. This observation raises the question of whether IL-6 blockade is effective only in patients with elevated serum IL-6 levels. If so, IL-6 measurement may be an indispensable part of the grading system. Moreover, the IL-6 level alone may not be sufficient to reflect its functional downstream effects [52]. An assay that distinguishes functional IL-6 from total IL-6 may provide a refined approach to guide therapeutic decisions. C-reactive protein (CRP), an acute-phase inflammatory protein synthesized by IL-6-dependent hepatic biosynthesis, is a reliable marker of IL-6 bioactivity and is used to predict CRS severity and monitor IL-6 blockade efficacy for patients with CAR T cell-induced CRS [10,12]. The CRP level in virus-induced CRS remains to be determined. Most studies suggested that elevated CRP levels were associated with severe COVID-19 [37,53,54], with a few exceptions [35]. Nevertheless, future studies on biomarkers are needed for the purpose of risk stratification and therapeutic effect monitoring. There is also a battery of biological agents available that target various critical molecules in the inflammatory network (Table 2), such as IL-1, IL-18, TNF, and IFN, or Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling. These agents may also be beneficial, and if so, routine inflammatory cytokine measurement is warranted.

Notably, SARS-CoV, MERS-CoV and SARS-CoV-2 were all considered to have originated in bats, a nature reservoir of various coronavirus species with high genomic diversity [55,56]. It is unclear how many bat coronaviruses are directly or indirectly transmissible to humans and how many have the potential to cause disease, especially for those that share the viral spike sequence and are capable of using the human ACE2 receptor for entry [55]. Thus, it is highly likely that a novel bat coronavirus could cause future epidemics. For future epidemic preparedness and to reduce mortality in COVID-19 patients, global effort is needed to promote novel therapy to treat virus-induced CRS during the COVID-19 outbreak. Potential therapies available for CRS are summarized in Table 2. We hope that this assessment will spur future clinical trials on COVID-19-induced CRS. Utilizing biologicals such as tocilizumab to treat virus-induced CRS is a new field. Many other therapeutic options, including hydroxychloroquine combined with azithromycin (NCT04322123, NCT04321278) [57], mesenchymal stem cell therapy (NCT04269525, NCT04252118) and convalescent plasma (NCT04292340), have moved into clinical trials for COVID-19. We look forward to seeing additional exciting progress and clinical evidence in this area.

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Author contributions

B.L searched literatures, B.L, Y.X and X.G drafted the manuscript, Y.X, X.G, M.L and Z.Z. discussed and revised the manuscript.

Declaration of competing interest

No potential conflicts of interest relevant to this review were reported.

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