Interleukin-6 signaling blockade treatment for cytokine release syndrome in COVID-19 (Review)

JIA-JIE CHEN[1*], LI-NA ZHANG[1*], HU HOU[2], LINGQING XU[3] and KUNMEI JI[1]

[1]Department of Biochemistry and Molecular Biology, Health Science Center of Shenzhen University, Shenzhen, Guangdong 518060; [2]Department of Clinical Laboratory, Shenzhen People's Hospital, Shenzhen, Guangdong 518020; [3]Department of Clinical Laboratory, The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan, Guangdong 511518, P.R. China

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Abstract. A severe immune response in patients with coronavirus disease 2019 (COVID-19) can cause a potentially lethal unconstrained inflammatory cytokine storm, known as cytokine release syndrome (CRS). The present study provides an overview of the biology underlying CRS and how targeted inhibition of interleukin (IL)-6 signaling may improve outcomes and the survival of patients suffering from COVID-19. Preliminary clinical results have indicated that antagonism of the IL-6 receptor (IL-6R), including with the FDA-approved humanized monoclonal antibody tocilizumab, can improve the outcomes of patients with severe or critical COVID-19 while maintaining a good safety profile. The available clinical data support the expansion of clinical trials using IL-6R targeting inhibitors for severe and critical COVID-19 treatment.

Contents

Correspondence to: Dr Lingqing Xu, Department of Clinical Laboratory, The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People's Hospital, B24 Yinquan Road, Qingyuan, Guangdong 511518, P.R. China
E-mail: lingqing_xu@126.com

Professor Kunmei Ji, Department of Biochemistry and Molecular Biology, Health Science Center of Shenzhen University, 1066 Xueyuan Road, Nanshan, Shenzhen, Guangdong 518060, P.R. China
E-mail: jkm@szu.edu.cn

*Contributed equally

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1. Introduction

As of May 2020, 300,000 people had died of coronavirus disease 2019 (COVID-19) worldwide, with cases still on the rise in a number of countries (1-3). The 2019 novel coronavirus, subsequently designated assevere acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), identified in samples of bronchoalveolar lavage fluid from patients with COVID-19, was confirmed as the cause of the COVID-19 pandemic (2). The analysis of genome sequencing indicated that SARS-CoV-2 is a betacoronavirus 2b lineage associated with human SARS and Middle East respiratory syndrome (MERS) (2). The fast spread of the COVID-19 suggests that SARS-COV-2 is highly contagious (3). Commonly, patients with COVID-19 experience fever, cough, myalgia and fatigue. Although the majority patients recover from COVID-19, as many as 20% develop serious complications, including acute respiratory distress syndrome, which may quickly deteriorate into respiratory failure, or even multiple organ dysfunction syndrome, and may need to be transferred to an intensive care unit (ICU) (1). At present, there are no effective therapies or vaccines for COVID-19 (3). There remains an urgent requirement to identify effective treatment strategies for COVID-19 that can reduce mortality risk in affected patients.

2. The peril of cytokine storms in COVID-19

Although the factors underlying COVID-19 presentation variability are still being elucidated, it is believed that disease severity is related to a virus-induced cytopathic effect and whether there is viral escape of the host immune response (4). A severe host immune response can cause lethal tissue lesions and an unconstrained inflammatory cytokine storm, known as cytokine release syndrome (CRS), as has been seen in patients infected with other coronaviruses, such as those identified as the pathogens that cause SARS and MERS (5).

Patients with COVID-19, especially those requiring ICU admission, have been reported to exhibit increased plasma levels of inflammatory cytokines, including interleukin (IL)-6,

IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-γ inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein 1α and tumor necrosis factor α (6). Histology of biopsy samples obtained from patients who suffered mortality due to COVID-19 has revealed bilateral diffuse alveolar injury accompanied by cell-fibromyxoid exudates with inflammatory infiltration of interstitial mononuclear cells, predominantly lymphocytes (7). Given the histological observations that evidence CRS in critical and lethal COVID-19, it can be suggested that therapeutic interventions that dampen inflammatory cytokine signaling may alleviate inflammation and reduce mortality in COVID-19.

3. IL-6 signaling and inflammatory storms

Elevated IL-6 is a pronounced and causative factor of CRS in patients, including CRS in patients with SARS or MERS (8). Serum IL-6 levels have been related associated with CRS severity in patients with SARS. In one report, serum IL-6 levels were indicated to reach 517±796 pg/ml in patients suffering severe SARS, and then to decrease gradually down to 68.8±25.9 pg/ml as patients recovered (9). In addition, in a study using a mouse model of CRS and CRS-induced neurotoxicity, monocyte-derived IL-6 was demonstrated to be required for the development of CRS and associated neurotoxicity during the administration of chimeric antigen receptor T-cell immunotherapy (10). Specifically, suppression of serum IL-6 levels was associated with an alleviation of CRS and neurotoxicity in the CRS model mice (10).

IL-6 activates downstream pathways primarily via a classic cis-signaling and trans-signaling pathway (11). In the cis-signaling pathway, a complex of IL-6 with the widely expressed gp130 protein binds the membrane-bound IL-6 receptor (mIL-6R), which is expressed selectively on immune cells. This triggers transduction via a Janus kinase (JAK) and STAT3 protein mediated signaling pathway (12). Activation of the IL-6 cis-signaling pathway has multiple effects on both the acquired (B and T cells) and innate (neutrophils, macrophages and natural killer cells) immune systems, which may contribute to the development of CRS (13). In the trans-signaling pathway, high levels of IL-6 bind soluble IL-6Rs, forminga complex with gp130 dimers on cell surfaces and thereby inducing downstream JAK-STAT3 signaling in a variety of cell types, including endothelial cells (14). Activation of this IL-6 trans-signaling pathway can lead directly to a systemic cytokine storm, including the secretion of VEGF (vascular endothelial growth factor), monocyte chemoattractant protein-1, IL-8 and IL-6, while also causing an increase in the expression of E-cadherin (15). VEGF and E-cadherin increase vascular permeability and leakage, leading to pathophysiological processes that underlie lung dysfunction in lower respiratory disease (15).

4. Inhibition of IL-6 signaling

There are two main types of IL-6 signaling inhibitors available, those that target IL-6 and those that target IL-6R (Fig. 1). IL-6 signaling can be targeted using monoclonal antibodies, including siltuximab, sirukumab, olokizumab, clazakizumab and satralizumab (16,17). Siltuximab was approved by the US FDA in 2014 as a humanized antibody drug for the treatment of multicentric Castleman disease (16). Although other IL-6 targeting antibodies have been indicated to inhibit IL-6 associated inflammation in clinical studies, their safety remains undetermined (16). For example, in a phase 3 clinical trial of sirukumabfor the treatment of arthritis (registration no. NCT01856309), an increased number of deaths occurred in the sirukumab treatment group compared with the placebo group, most often due to a major cardiovascular adverse event. This outcome led the US FDA not approving the clinical use of sirukumab for arthritis. Similarly, a trial of the clazakizumab was also terminated due to adverse events in aphase 2 clinical trial for the treatment of arthritis (registration no. NCT02015520). Olokizumab is currently being examined in a phase 3 clinical trial for the treatment of arthritis (registration no. NCT02760433), and a phase 3 clinical trial of satralizumab for the treatment of optic neuromyelitis spectrum disorder has yielded positive results (registration no. NCT02028884) (17).

IL-6 signaling has diverse biological functions, including the mediation of a protective feedback effect on tissue damage (18). In an experimental acute respiratory distress syndrome model of primary direct viral lung infection (as opposed to infection outside of the lungs), IL-6 blockers have been demonstrated to increase mortality, mainly due to reduced autophagy and increased pulmonary fibrosis (19). In addition, loss of IL-6 can lead to systemic insulin resistance in mice (20). Therefore, due to the fact IL-6 targeting inhibitors may cause an adverse reaction, translation of such agents into clinical applications requires close attention and thorough investigation.

The IL-6R targeting humanized monoclonal antibodies tocilizumab and sarilumab have been approved by the US FDA for the treatment of rheumatoid arthritis (21). Additionally, owing to its pronounced inflammation inhibiting effects, tocilizumab has been approved for use in chimeric antigen receptor T-cell therapy for systemic juvenile idiopathic arthritis and B-precursor acute lymphoblastic leukemia-associated CRS (22). Tocilizumab acts as a competitive antagonist for soluble and membrane-bound forms of IL-6R, thereby inhibiting both cis- and trans-signaling pathways and, consequently, reducing inflammatory activity (23). Compared with IL-6 inhibitors, IL-6R inhibitors have been demonstrated to exhibit a high level of safety in clinical studies (24-26). Long-term animal toxicity testing has indicated that tocilizumab is well tolerated by body systems, with no obvious abnormalities being observed in opportunistic histopathology (24-26). Potential uses of tocilizumab in ovarian (27), pancreatic (28) and colorectal cancer (29) are also being examined. A combination of tocilizumab with carboplatin and/or doxorubicin has indicated good feasibility and safety in a phase 1 clinal trial for the treatment of ovarian cancer (30). Therefore, it is reasonable to examine whether the IL-6R targeting inhibitor tocilizumab may be used to inhibit CRS and alleviate disease severity in patients with COVID-19.

5. Clinical trials of tocilizumab treatment for COVID-19

With respect to the development of CRS in patients with COVID-19, Zhou *et al* (31) reported that serum IL-6 levels

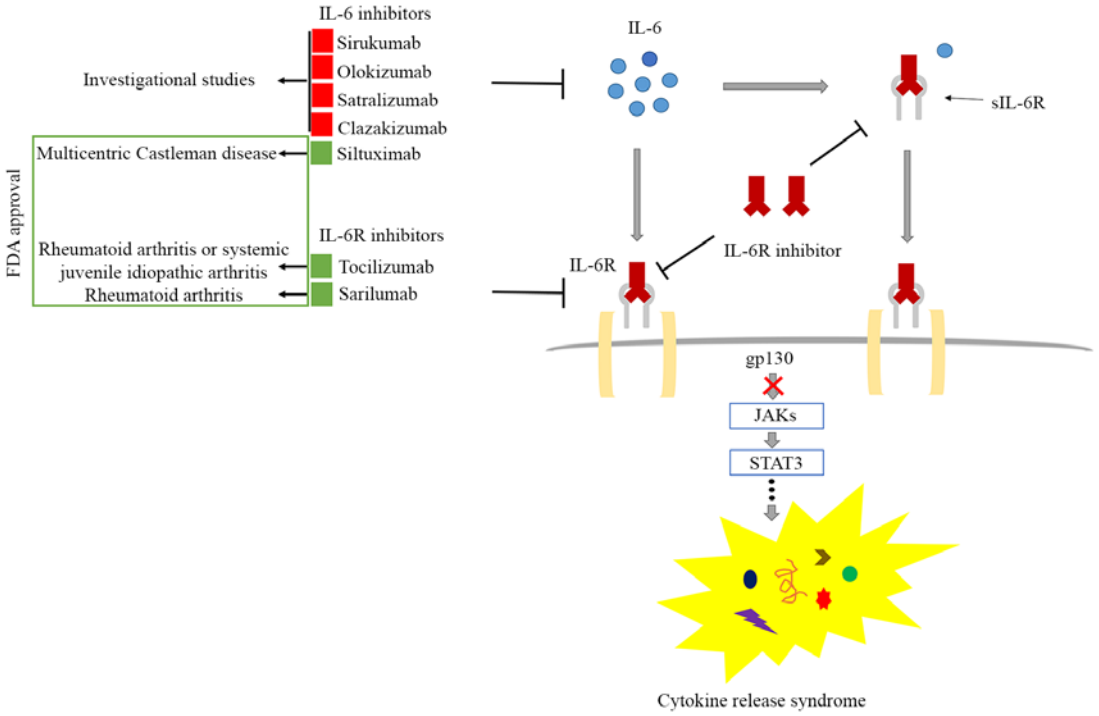

Figure 1. Actions of IL-6 and IL-6R inhibiting monoclonal antibodies on cytokine release-mediated inflammatory storms. The US FDA status of investigational drugs are shown with a green (approval) or red (rejection) box. The inhibitors suppress IL-6 signaling by impeding gp130 mediated activation of JAK and STAT3 signaling, thereby inhibiting cytokine-mediated inflammation and alleviating CRS. IL, interleukin; JAK, Janus kinase; sIL, soluble interleukin; glycoprotein 130, gp130.

in patients with COVID-19 (n=33) were increased due to significantly increased proportions and numbers of inflammatory $CD14^+$ $CD16^+$ monocytes. As aforementioned, histology of autopsy samples from patients who have succumbed to COVID-19 revealed bilateral diffuse alveolar injury and cellular fibromyxoid exudates that are consistent with CRS (6). A total of 26 clinical investigations of tocilizumab treatment (commonly, 8 mg/kg intravenously) for COVID-19 were registered between January to May 2020 (ClinicalTrials.gov) and the Chinese Clinical Trial Registry (chictr.org.cn), including 23 intervention trials and 3 observation trials (Table I). Some trials have only included patients with very high serum IL-6 levels, such as >7 or 40 pg/ml (32-36). Xu *et al* (32) reported an encouraging alleviation of clinical symptoms of COVID-19. In the aforementioned study, a total of 21 patients with COVID-19 (including 17 with severe disease and 4 with critical disease) who presented with fever as their first symptom (mean body temperature, 38.8±0.6˚C), and whose symptoms did not improve in response conventional treatment, exhibited encouraging responses to tocilizumab treatment. The patients exhibited varying degrees of deterioration, persistent fever, hypoxemia and pulmonary lesion worsened while receiving conventional treatment (mean time, 5.6 days), but within 1 day of starting tocilizumab treatment, all exhibited some alleviation of fever, with some patients returning to a normal body temperature, and the majority of patients experiencing an improvement in respiratory function and chest tightness. Within 5 days of starting the tocilizumab treatment, inflammation indicators (for example, peripheral blood lymphocyte counts and C-reactive protein levels) had mostly recovered and 15/20 patients required less oxygen support to sustain their oxygen saturation (1 patient refused oxygen support), including 2 patients who were withdrawn from mechanical ventilation (32). All 21 patients recovered and were discharged from the hospital an average of 15.1 days after beginning tocilizumab therapy, with no incidences of adverse drug reactions or secondary lung infections (32).

A number of studies have demonstrated that tocilizumab treatment is effective in patients with COVID-19. In a retrospective study conducted through a chart review, 239 patients with COVID-19, including 135 with non-severe disease and 104 with severe disease, who at some point in the course of their disease developed signs of CRS, were treated with tocilizumab (33). Among patients treated with tocilizumab and required mechanical ventilation, the survival rate was 75% (33). After commencement of tocilizumab treatment, very few adverse reactions occurred, which included increased high-sensitivity C-reactive protein levels and oxygen requirements, and the patients' oxygenation and inflammation biomarkers consistently improved (33). The survival rate among patients treated with tocilizumab and with severe disease (83%) was statistically similar to that of patients with non-severe disease (91%) (33). A single-center study of a prospective series of 100 patients diagnosed with COVID-19 pneumonia reported that 32 of 43 patients in ICU exhibited rapid and sustained clinical improvement in response to tocilizumab treatment (34). Additionally, tocilizumab was demonstrated to shorten clinical improvement time in a retrospective cohort study (35). Another retrospective cohort study indicated that tocilizumab administration was associated with reduced duration of hospitalization, ICU admission and mechanical ventilation inpatients with COVID-19 (36).

Table I. Clinical trials of tocilizumab (Toc) for patients with COVID-19 from January to May of 2020.

Identifier	Study type	Intervention model	Intervention	Phase	IL-6 level	N	Location
ChiCTR2000029765	Interventional	Randomized, parallel asnmt	Toc 4-8 mg/kg IV	4	>7 pg/ml	94	China
NCT04377750	Interventional	Randomized, parallel asnmt	Toc 8 mg/kg IV	4	-	500	Israel
NCT04345445	Interventional	Randomized, crossover asnmt	Toc 8 mg/kg IV	3	-	310	Malaysia
NCT04320615	Interventional	Randomized, DB, multicenter, parallel asnmt	Toc 8 mg/kg IV	3	-	330	USA
NCT04372186	Interventional	Randomized, DB, multicenter, parallel asnmt	Toc 8 mg/kg IV	3	-	379	-
NCT04361032	Interventional	Randomized, multicenter, parallel asnmt	Toc 8 mg/kg IV	3	-	260	Tunisia
NCT04356937	Interventional	Randomized, DB, single-center, parallel asnmt	Toc 8 mg/kg IV	3	-	300	USA
NCT04361552	Interventional	Randomized, parallel asnmt	Toc IV	3	-	180	USA
NCT04317092	Interventional	Multicenter, single group asnmt	Toc 8 mg/kg IV/12 h	2	-	400	Italy
NCT04377659	Interventional	Randomized, parallel asnmt	Toc 8 mg/kg IV	2	≥80 pg/ml	40	USA
NCT04331795	Interventional	Non-randomized, single group asnmt	Toc 200 mg	2	-	50	USA
NCT04335071	Interventional	Randomized, DB, multicenter, parallel asnmt	Toc 8 mg/kg IV	2	-	100	USA
NCT04346355	Interventional	Randomized, multicenter, parallel asnmt	Toc 8 mg/kg IV/12 h	2	-	398	Italy
NCT04363736	Interventional	Randomized, multicenter, parallel asnmt	Toc 8 mg/kg IV	2	-	100	-
NCT04377503	Interventional	Randomized, crossover asnmt	Toc 8 mg/kg IV per 12 h	2	>7 pg/ml	40	-
NCT04363853	Interventional	DB, single group asnmt	Toc	2	-	200	Mexico
NCT04370834	Interventional	Single group asnmt	Toc IV	2	-	200	-
NCT04315480	Interventional	Single group asnmt	Toc 8 mg/kg IV	2	-	38	Italy
NCT04333914	Interventional	Randomized, multicenter, parallel asnmt	Toc 400 mg IV	2	-	273	France
NCT04331808	Interventional	Randomized, parallel asnmt	Toc 8 mg/kg IV	2	-	228	France
NCT04332094	Interventional	Randomized, multicenter, parallel asnmt	Toc 162 mg sc 2x 12 h interval	2	-	276	Spain
NCT04310228	Interventional	Randomized, multicenter, parallel asnmt	Toc 4-8 mg/kg IV	-	>7 pg/ml	150	China
ChiCTR2000030442	Interventional	Non-randomized asnmt	Toc	-	-	100	China
NCT04359667	Observational	Case-only study	Toc 8 mg/kg IV	-	-	30	Croatia
NCT04332913	Observational	Cohort study	Toc 400 mg IV	-	>40 pg/ml	30	Italy
NCT04306705	Observational	Cohort study	Toc 8 mg/kg IV	-	≥3x normal UL	120	

Information from ClinicalTrials.gov registration (website: https://clinicaltrials.gov) and Chinese Clinical Trial Registry (ChiCTR, website: https://www.chictr.org.cn).. Asnmt, assignment; DB, double-blinded; Toc, tocilizumab; IV, intravenous injection; sc, subcutaneous; UL, upper limit; N, numbers.

Additionally, tocilizumab has been demonstrated to be well tolerated and to be free of clinically significant adverse events while prohibiting disease progression in hospitalized patients with moderate COVID-19 and excessive inflammation (37).

Although limited in scope, these data suggest that tocilizumab can improve the prognosis of severe and critical patients with COVID-19, including reducing mortality. Follow-up studies are currently examining the effectiveness of tocilizumab for COVID-19, including clinical trials in Italy and France (38). Based on encouraging data and observations with tocilizumab, the National Health Commission of the People's Republic of China has declared officially that tocilizumab can be provided to patients with COVID-19 who exhibit extensive bilateral lung lesions opacity and to those in severe or critical condition with increased serum IL-6 levels (39).

6. Conclusion

In the context of an ongoing urgent requirement for an effective COVID-19 treatment, a promising strategy of controlling CRS has emerged. Preliminary clinical results have indicated that antagonism of IL-6R with tocilizumab can improve the outcomes of patients with severe or critical COVID-19 while maintaining a good safety profile. The data obtained so far supports the expansion of clinical trials of IL-6R targeting inhibitors, such as tocilizumab, for severe and critical COVID-19 treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

JJC and KJ conceived and designed the study. JJC and LNZ performed the literature review. JJC and LNZ wrote the manuscript. HH, LX and KJ revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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