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A Comprehensive Review of Tocilizumab in COVID-19 Acute Respiratory Distress Syndrome

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Abstract

Currently, the world is facing the pandemic of a novel strain of beta-coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Acute respiratory distress syndrome (ARDS) is the most devastating complication of SARS-CoV-2. It was indicated that cytokine-release syndrome and dominantly interleukin (IL)-6 play a central role in the pathophysiology of ARDS related to the novel 2019 coronavirus disease (COVID-19). Despite the global emergency of the disease, at this time, there are no proven therapies for the management of the disease. Tocilizumab is a potential recombinant monoclonal antibody against IL-6 and currently is under investigation for the management of ARDS in patients with COVID-19. Given these points, we reviewed the current evidence regarding the potential therapeutic role of tocilizumab and its important clinical issues in the treatment of ARDS related to COVID-19.

Keywords

acute lung injury, ARDS, CRS, COVID-19, IL-6, SARS-CoV-2, tocilizumab

Coronaviruses are a large family of RNA viruses which are widely found in nature. Generally, coronaviruses are animal pathogens, but in humans, 6 types of coronaviruses are known to cause respiratory tract infections ranging from mild to severe disease. The outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 were 2 severe types of infections caused by beta-coronaviruses with 11%-35% mortality.[1-3]

Late in December 2019, a novel strain of beta-coronavirus was recognized to cause a cluster of cases of acute pneumonia in Wuhan, Hubei province, China. Unlike with SARS-CoV and MERS-CoV, the novel virus has a lower rate of mortality, but a higher rate of transmissibility and infectivity, rapidly spreading throughout the globe. The World Health Organization (WHO) declared a pandemic outbreak and named the disease coronavirus disease 2019 (COVID-19), along with the International Committee on Taxonomy of Viruses, which called the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the time of writing this article, globally more than 7 410 000 confirmed cases of COVID-19 with more than 418 000 deaths have been reported.[1-3]

Person-to-person spread is the main route of viral transmission, which occurs by respiratory droplets. Notably, inhaled aerosols are another proposed pathway for transmission of SARS-CoV-2. It has been indicated that viable viruses could be detected in aerosols up to 3 hours after aerosolization. Transmission of the virus can take place with contact of contaminated surfaces or objects with the eyes, nose, and mouth.[4,5]

Classically, the well-known symptoms of COVID-19 include fever, cough, and shortness of breath. A recently pooled meta-analysis of 43 studies involving 3600 patients with COVID-19 showed that the most common clinical manifestations of the disease were fever (83.3%; 95%CI, 78.4%-87.7%), followed by cough (60.3%; 54.2%-66.3%), fatigue (38.0%; 29.8%-46.5%), myalgia (28.5%; 21.2%-36.2%), increased sputum production (26.9%; 18.3%-36.4%), chest pain (14.9%; 4.9%-28.4%), chills (15.0%; 0.3%-41.4%), headache (14%; [9.9–18.6]), sore throat (12.3% [%8.5–%16.5]), dizziness (7.6% [%0.0–%23.5]), and

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diarrhea (8.4%; 4.8%-12.6%). A recent observational study of 2013 European patients with mild to moderated COVID-19 reported the loss of smell and taste dysfunction in 87% and 56% of patients, respectively. Accordingly, the Centers for Disease Control and Prevention has added 6 new symptoms including new loss of taste or smell, muscle pain, headache, chills, repeated shaking with chills, and sore throat to its list as other symptoms of COVID-19.[6-9]

Acute respiratory distress syndrome (ARDS) is the most devastating complication of SARS-CoV-2, with a higher death toll. In a meta-analysis study, ground-glass opacity (80%; 67.3%-90.4%), >3 affected lobes (57.3%; 42.6%-71.4%), and fibrous stripes (25.9%; 2.9%-59.8%) were common chest computed tomography (CT) findings. Moreover, the incidence of ARDS and death was 15.7% (5.0%-30.4%), and 3.6% (1.1%-7.2%), respectively. The incidence of ARDS following COVID-19 is higher in severe cases. For example, in a study of 52 critically ill patients, 67% (35 patients) developed ARDS with a higher mortality rate (32 patients died).[6,8]

Cytokine-release syndrome (CRS) in its severe form is a life-threatening acute systemic inflammatory syndrome characterized by multiorgan damage and fever. It has been indicated to have a central role in the development of ARDS following SARS-CoV-2 infection. Interleukin 6 (IL-6) has been shown to play the key role in COVID-19-induced CRS, and its elevated levels have been observed in these patients.[10-12] Despite the global emergency of the disease, currently, there are no proven therapies for the management of the disease. Most of the treatments are undergoing clinical trials and mainly include antiviral or anti-inflammatory medications or conservative therapies.

Tocilizumab, sarilumab, and siltuximab are commercially available IL-6 inhibitors. They are under investigation for the management of ARDS induced by COVID-19. Tocilizumab is a recombinant humanized monoclonal antibody that binds to both membrane-bound and soluble forms of the IL-6 receptor. Labeled indications for tocilizumab include rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, giant-cell arteritis (GCA), and chimeric antigen receptor (CAR) T-cell-induced severe CRS. Furthermore, it is used in the treatment of severe CRS because of bispecific T-cell engager (BiTE) therapy. Sarilumab is a fully human immunoglobulin G1 monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors with high affinity and is Food and Drug Administration (FDA)-approved for the treatment of RA. Siltuximab is a chimeric, human-murine immunoglobulin monoclonal antibody that binds directly to human IL-6 to neutralize it. The only labeled indication of siltuximab is for the treatment of Castleman disease. Tocilizumab is the first marketed IL-6 blocker that has been widely used in the treatment of patients with inflammatory diseases. Importantly, it is the only monoclonal antibody drug with FDA approval for the treatment of CAR T-cell-induced CRS.[1-6,12,13]

Based on the potential role of tocilizumab in the management of CRS, the main role of IL-6 in CRS, and the marked role of CRS in the pathophysiology of ARDS of SARS-CoV-2, we aimed to review the current evidence concerning the safety and efficacy of the use of tocilizumab in the management of ARDS in patients with COVID-19.

Pathophysiology

Mechanism of Cell Entry of SARS-CoV-2

The SARS-CoV-2 spike glycoprotein (S) binds the host cell surface via angiotensin-converting enzyme-2 (ACE-2) receptor, allowing virus cell entry and replication.[14] It has been indicated that SARS-CoV-2 recognizes the human ACE-2 receptor more efficiently than SARS-CoV. Moreover, it has a strong binding affinity to the human ACE-2 receptor.[10] Expression of the ACE-2 receptor is found in the heart, kidney, endothelium, and intestine, with a higher ratio in pulmonary tissues.[1,15-20] Evaluating normal lung tissue from 8 adult donors showed that 83% of ACE-2-expressing cells were alveolar epithelial type II cells. Accordingly, these cells are a reservoir for SARS-CoV-2 invasion.[15]

SARS-CoV-2-Induced Lung Injury

The pathological features of SARS-CoV-2 are similar to SARS-CoV and MERS-CoV infections.[21] Furthermore, the envelope proteins (E proteins) involved in the viral assembly of SARS-CoV-2 and SARS-CoV share 95% homology and mediate the host immune reaction to coronaviruses.[22,23] It is believed that the delayed type I interferon (INF) response plays a role in the process of SARS-CoV infection. In the initial phase, the virus evades pattern-recognition receptors and antagonizes the type I INF response in the airway and alveolar epithelial cells, which leads to rapid viral replication. However, plasmacytoid dendritic cells and macrophages' response to SARS-CoV leads to a strong but delayed type I INF response as well as releasing other inflammatory cytokines. The activation of type I INF signaling cascades attracts neutrophils, inflammatory monocyte-macrophages, dendritic cells, and natural killer (NK) cells to the lung, and a cytokine-driven vicious cycle occurs. The uncontrollable proinflammatory cytokine production such as IL-6 leads to diffuse alveolar damage with epithelial and endothelial apoptosis, dysregulated coagulation, and pulmonary fibrinolysis.[24-27] In some cases of SARS-CoV, it was shown that ARDS can take place independently of viral load, suggesting the important role of inherent

properties of the host immune system rather than viral virulence on tissue.[1,5,28]

SARS-CoV-2 activates the immune system through binding to the alveolar epithelial cells and leads to the release of cytokines, mainly IL-6. Consequently, alveolar-capillary permeability to fluid, proteins, and blood cells is increased, and respiratory failure occurs.[29-31] Evaluating the immune system of patients with COVID-19 showed that activation of abnormal pathogenic T cells leads to the production of a large number of cytokines, importantly IL-6, as well as induction of an inflammatory storm. In addition to IL-6, higher plasma levels of other cytokines including, IL-2, IL-7, IL-10, tumor necrosis factor-α (TNF-α), macrophage inflammatory protein-1 alpha, granulocyte colony-stimulating factor, interferon-γ-inducible protein-10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1) were observed in intensive care unit (ICU) patients. Furthermore, IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) play the key roles in the inflammatory storm, which probably leads to pulmonary fibrosis and organ failure through impairment of gas exchange across the alveolar-capillary membrane.[10,11]

Analyzing peripheral blood samples indicated that T cells and monocytes in severe/critical COVID-19 patients are significantly lower than in healthy patients. Moreover, inflammatory monocytes with the CD14+CD16+ phenotype and high IL-6 expression as well as pathogenic Th1 cells with high expression of GM-CSF and IFN-γ exist in both peripheral blood and biopsy samples at autopsy of COVID-19 patients. Indeed, these inflammatory monocytes and pathogenic T cells stimulate the immune system and cause end-organ damage.[32] Postmortem examination of a patient who died of confirmed infection with COVID-19 demonstrated bilateral diffuse alveolar damage with cellular fibromyxoid exudates. In addition, mononuclear inflammatory lymphocytes were observed in both lungs. Moreover, the characteristic viral cytopathic changes such as multinucleated syncytial cells with atypical enlarged pneumocytes in the intra-alveolar spaces were observed.[33]

Interleukin 6 and Cytokine-Release Syndrome (CRS)

IL-6 is a multifunctional cytokine and has an important role in acute inflammation.[34] It has an essential role in the differentiation of B cells and the production of antibodies.[35] IL-6 is a proinflammatory regulator of T cells that induces cytotoxic T-lymphocyte activity, stimulates T-helper 17 cell lineage, function, and the development of self-reactive proinflammatory CD4 T-cell response, and inhibits the induction of regulatory T-cell stimulate.[36-38] Also, IL-6 stimulates the differentiation of osteoclasts and angiogenesis.[39]

CRS is a severe and life-threatening acute systemic inflammatory syndrome characterized by multiorgan damage and fever that often takes place in patients receiving immunotherapy or haploidentical allogeneic hematopoietic cell transplantation and is associated with a sharp increase of inflammatory cytokine levels; however, it can occur via viral infections. Clinical manifestations can range from a flu-like syndrome to circulatory collapse, pulmonary edema, hypoxia, peripheral edema, hypotension, and multiorgan system failure.[40-43]

In the pathogenesis of T-cell-engaging immunotherapy, released INF-γ by activated T cells activates macrophages. Afterward, the activated macrophages release TNF-α, IL-6, and IL-10. Furthermore, serum levels of IL-8, IL-5, and IL-1 are elevated in CSR and are thought to contribute to its clinical manifestations. TNF-α is associated with flu-like symptoms as well as malaise, fever, diarrhea, lung damage, cardiomyopathy, and vascular leakage. INF-γ is associated with fatigue, dizziness, headache, fever, and chills, and IL-6 is associated cardiomyopathy, activation of the complement and coagulation cascades, cardiomyopathy, and disseminated intravascular coagulation.[44-48] In CAR T-cell therapy-associated CRS, IL-6 is considered a key driver symptom, and its levels increase dramatically (more than 100-fold). No studies have been carried out to evaluate the effects of tocilizumab for CAR-T-associated CRS; however, rapid clinical improvement in several patient cohorts led to rapid FDA approval in August 2017. Also, tocilizumab is used in the treatment BiTE therapy induced severe CRS.[49,50]

IL-6 plays an important role in the inflammatory storm in patients with COVID-19, and combining antiviral with anti-inflammatory treatments should be considered.[51,52] A study by Wang et al showed that all 11 critically ill patients had a significant increase of IL-6 as an early indicator of CRS-like reactions in COVID-19-infected pneumonia. It was found that 72.7% of patients had CRS-like characteristics such as fever, pulmonary inflammation, an increase in IL-6, and multiorgan dysfunction.[53] Another study in patients with COVID-19 found that high levels of IL-6 are associated with the severity of pneumonia.[54] In addition, a retrospective multicenter study of 150 patients with COVID-19 pneumonia showed elevated levels of inflammatory factors such as ferritin ($P < .001$) and IL-6 ($P < .0001$) in the blood are predictors of mortality outcome.[55] CAR T-cell-induced CRS and the role of IL-6 briefly are shown in Figure 1.

It has been indicated that levels of cytokines including IL-6, IL-2, IL-1β, IL-8, IL-17, IFN-γ, TNF-α, IL-4, IP-10, and MCP-1 are elevated in patients with COVID-19.[56] Consequently, in addition to IL-6, other inflammatory cytokines have a crucial

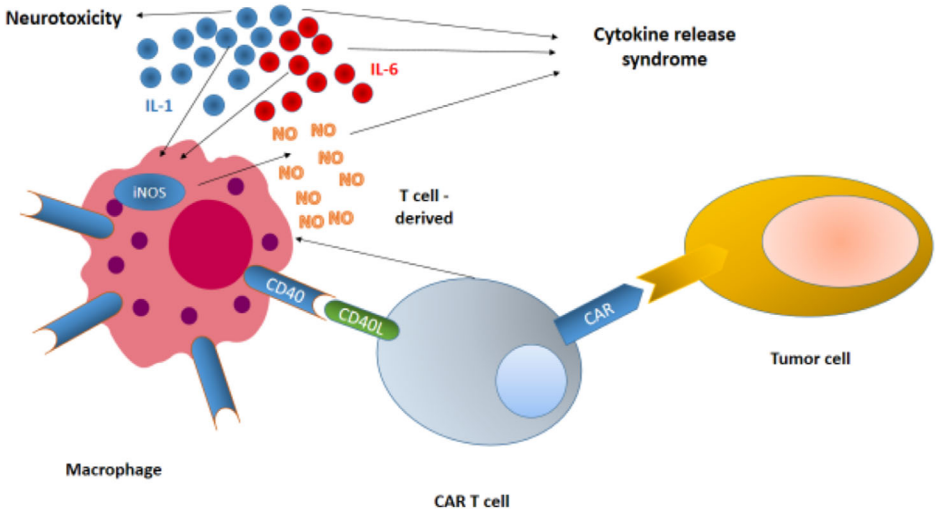

Figure 1. Interleukin 6 role in chimeric antigen receptor T-cell-induced cytokine-release syndrome.

role in the development of CRS. It was shown that total T cells, CD4+ T cells, CD8+ T cells, and NK cell numbers were significantly lower in severe/critical COVID-19 compared with mild patients and healthy subjects. Also, features of cellular abnormality and exhaustion have been observed in T cells and NK cells. In addition, therapies that act more generally such as corticosteroids might reduce the immune system. These drugs suppress immune cells, especially CD4 and CD8 T cells. Therefore, some guidelines on COVID-19 treatment such as those of Massachusetts General Hospital recommend that systemic steroids should be avoided in patients with COVID-19, but they may be used for other reasons such as refractory septic shock. In addition, the national institution health treatment guidelines for COVID-19 recommend a low-dose of corticosteroids in patients with COVID-19 and refractory shock. A multicenter quasi-experimental study in 213 patients with moderate to severe COVID-19 showed that early administration of methylprednisolone (0.25-0.5 mg/kg) twice daily for 3 days is associated with improved clinical outcomes. Indeed, the occurrence of the composite end point was significantly lower in the early corticosteroid-received group compared with the nontreated group (34.9% vs 54.3%, $P = .005$). Moreover, a single-center retrospective cohort study was done in 463 patients with COVID-19 pneumonia to determine the role of steroids in inhospital mortality. Results indicated that the survival rate was higher in patients who received glucocorticoids compared with those who did not. Furthermore, no statistically significant difference was observed in the mortality rate between the initial regimens of methylprednisolone (1 mg/kg/day) or the equivalent and pulses of glucocorticoids. In contrast to these reports, a meta-analysis pooling 11 reports of SARS-CoV-, MERS-CoV-, and SARS-CoV-2-infected patients indicated that corticosteroids delay virus clearance, increase the mechanical ventilation rate, prolong hospitalization, and have no significant effect on mortality. Therefore, considering the key role of IL-6 in COVID-19-induced CRS, suppression of IL-6 governs the immune response; using tocilizumab allows other immune responses to fight COVID-19 and protects against the harmful effects of hyperinflammation.[57-62] Screening for hyperinflammation is suggested in patients with COVID-19. For example, ferritin seems to be the diagnostic hallmark of macrophage activation syndrome and is elevated in a patient with severe COVID-19, especially in secondary hemophagocytic lymphohistiocytosis.[63] In a retrospective multicenter cohort study of 191 patients with COVID-19, serum levels of ferritin were significantly higher in nonsurvivors compared with survivors throughout the clinical course (1435.3 mg/L [728.9-2000.0 mg/L] vs 503.2 mg/L [264.0-921.5 mg/L]; $P \leq .0001$) and increased with disease deterioration.[56] As well, the mean serum level of ferritin in hemodialysis patients increased after infection with SARS-CoV-2, from 584 ± 318 to 1446 ± 1261 mg/L.[64]

Tocilizumab Potential for Use, Efficacy in COVID-19 Based on Published Data

Currently, data about the use of tocilizumab in COVID-19 are limited. Consequently, we are looking forward to seeing the results of ongoing trials to draw a conclusion. Along this line, 2 cases of successful treatment of COVID-19 in patients with malignant comorbidities have been reported with tocilizumab. The first patient with multiple myeloma was treated with a single dose of intravenous tocilizumab (8 mg/kg)

Table 1. Published Clinical Trials Investigating the Therapeutic Effect of Tocilizumab for the Treatment of COVID-19

Author, Year	Design	Country	Population (Sample Size)	Tocilizumab Dose	Other Treatments	Follow-up Days	Outcomes
Zhang et al, 2020	Case report	China	Respiratory failure (1)	IV; 8 mg/kg; 2 doses	Lopinavir-ritonavir	42	Fever resolution; DC of oxygen supplementation; radiological improvement in ground-glass changes—reduction from 225 to 33 mg/L
Michot et al, 2020	Case report	France	Respiratory failure (1)	IV; 8 mg/kg	Methylprednisolone, IV, 5 days	15	Resolution of chest symptoms; reduction of IL-6 levels to normal
Xu et al, 2020	Retrospective single-center case series	China	Severe or critical (21)	IV; 400 mg; 1 or 2 doses, 12-hour interval	Lopinavir methylprednisolone	NR	Fever resolution (100%); reduction of oxygen support (75%); radiological improvement (91%); lymphocytes return to normal (53%); CRP returning to normal (84%); 91% discharged; 9% remain stable
Luo et al, 2020	Retrospective single-center case series	China	Moderate, severe, or critical (15)	IV; 80-600 mg; 33% were administered subsequent doses	Methylprednisolone in 53% of patients	7	Death (20%); disease worsening (13%); clinical stability (67%); CRP reduced from 126.9 to 11.2 mg/L; drop in IL-6 (67%)
Sciascia et al, 2020	Prospective multicenter case series	Italy	Severe COVID-19 (63)	IV 8 mg/kg or SC 324 mg, 1 or 2 doses, ,24-hour interval.	Lopinavir/ritonavir in 71.4% of patients; darunavir/cobicistat in 28.6%.	14	No moderate to severe adverse events related to tocilizumab; significant improvement in ferritin, CRP, D-dimer, PaO_2/FiO_2 ratio; increase in likelihood of survival within 6 days.
Toniati et al, 2020	Prospective single-center case series	Italy	Severe COVID-19 (100)	IV 8 mg/kg, 2 doses, 12-hour interval; third dose is based on clinical response, 1-day interval	Lopinavir, ritonavir or remdesivir + hydroxychloroquine + dexamethasone + AB prophylaxis	10	Improving or stabilizing clinical condition in 77% of patients, worsening in 23% (20% died); lymphocyte count, CRP, fibrinogen, and ferritin serum levels improved; tocilizumab adverse effects: septic shock (2%), GI perforation (1%).
Moreno-García et al, 2020	Retrospective single-center, nonrandomized study	Spain	Non–critically ill COVID-19 patients (171)	IV 400 to 600 mg (based on weight), 1 to 3 doses based on response to treatment (in 77 patients)	Antiviral drugs, HCQ, azithromycin, LMWH (if risk factors for thrombosis), methylprednisolone (if disease progression to ARDS)	N/A	Reduction in ICU admissions and mechanical ventilation use, lower mortality (10.3%) than other reports.

IV, intravenous; DC, discontinuation; CRP, C-reactive protein; IL, interleukin; SC, subcutaneous; PaO_2/FiO_2, atrial partial pressure of oxygen/fraction of inspiration O_2, AB, antibiotic; GI, gastrointestinal; HCQ, hydroxychloroquine; LMWH, low-molecular-weight heparin; ARDS, acute respiratory distress syndrome.

on day 9 of hospitalization. Before treatment with tocilizumab, he received 40 mg methylprednisolone for 4 days. Despite improvement in breathing, chest tightness and CT imaging did not improve. After treatment of tocilizumab, serum level of the patient's IL-6 dropped from 122 to 21 pg/mL on day 18, and clinical symptoms and chest CT imaging both improved.[65] Another COVID-19 patient with a recent diagnosis of metastatic sarcomatoid clear-cell renal cell carcinoma received 2 doses of intravenous tocilizumab (8 mg/kg) with an 8-hour interval on hospital day 8, and the patient improved thereafter and recovered (Table 1).[66]

The published articles lack a clear analytical approach and show poor methodological quality. A retrospective single-center case series was carried out in 21 Chinese patients with critical (19%) and severe (81%) COVID-19. Critical COVID-19 was defined as requiring mechanical ventilation or organ support in the ICU. Severe COVID-19 included patients with tachypnea and/or respiratory failure. The mean age of patients was 56.8 ± 16.5 years, and

85.7 % of them were male. The mean level of IL-6 was 132.4 ± 278.5 pg/mL. All patients received standard care including lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy. In addition to standard care, all patients received a single dose of intravenous tocilizumab 400 mg, and 3 patients received a second administration of tocilizumab 400 mg with a 12-hour interval. It is important to mention that 7 days before treatment with tocilizumab, all the patients had received routine treatment; however, no improvement was observed in symptoms, hypoxemia, and CT images. Results showed immediate improvement of symptoms, CT opacity changes, and hypoxemia after tocilizumab administration. Patients' fever improved completely within 24 hours postadministration. Radiological improvement in ground-glass opacities took place in 91% of patients. Notably, blood and oxygenation results were reported in 19 patients. Mean C-reactive protein (CRP) level decreased from 75.1 ± 66.8 to 2.72 ± 3.6 mg/mL on day 5 after treatment. Furthermore, oxygen saturations of patients improved statistically significantly within 5 days after treatment. One patient no longer needed supplementary oxygen, 15 needed decreased oxygen support, 1 began the ventilator-weaning process, and 2 were extubated. Finally, 19 patients were discharged, and 2 were in stable condition in the hospital.[67] According to the National Health Commission of China, clinical classification of COVID-19 is as follow: mild, slight clinical symptoms but no imaging presentations of pneumonia; moderate, fever, respiratory symptoms, and pneumonia performance on chest x-ray or CT; severe, respiratory distress with respiratory rate > 30 times/min, or oxygen saturation at rest < 93%, or atrial partial pressure of oxygen/fraction of inspiration O_2 (PaO_2/FiO_2) ratio < 300 mm Hg (1 mm Hg = 0.133 kPa); critically severe, respiratory failure needs ventilation or shock, or combination with other organ failure, requirement for intensive care unit monitoring and treatment.[68] Another retrospective single-center case series was done in 15 Chinese patients who were moderately ill (13.3%), seriously ill (40%), and critically ill (46.7%) with COVID-19. The median age of patients was 73 years, with a male majority of 75%. Baseline comorbidities of patients included diabetes mellitus, hypertension, and previous cerebrovascular accident in 27%, 60%, and 20%, respectively. All patients were administered at least 1 dose of tocilizumab (80-600 mg) either alone (47%) or in combination with methylprednisolone (53%). Notably, 33% of patients received subsequent doses of tocilizumab. By day 7 posttreatment, 67% of patients were clinically stable, 13% had deterioration of their disease, and 20% died. The baseline levels of IL-6 ranged from 16.4 to 627.1 pg/mL. A mild rise of 74.8 pg/mL (-0.8-175.6 pg/mL) in median IL-6 level was observed after tocilizumab administration in 10 clinically stabilized patients, whereas the remaining 5 patients experienced a dramatic rise of 3581.2 pg/mL (591.9-4983.6 pg/mL); however, CRP levels rapidly, and significantly dropped, from 126.9 mg/L (10.7-257.9 mg/L) to 11.2 mg/L (0.02-113.7 mg/L) after tocilizumab administration ($P < .01$). This is in accordance with CRP being an appropriate surrogate marker for tocilizumab level and IL-6 bioactivity.[69]

A prospective multicenter case series was carried out in 63 patients with severe COVID-19. The mean age ± SD of the patients was 62.0 ± 12.5 years, and 88.8% were male. Patients with polymerase chain reaction-confirmed COVID-19, pulmonary involvement (oxygen saturation < 93% or PaO_2/FiO_2 < 300 mm Hg), and at least 3 of these criteria—lactate dehydrogenase (LDH) > 2 times the upper limit of normal; ferritin > 1000 mg/L; D-dimer > 10 times normal values; CRP > 10 times normal values—were included. Clinical and laboratory parameters were assessed at baseline and 14 days after treatment. Among 63 patients, 34 received intravenous tocilizumab (8 mg/kg), and 29 received subcutaneous tocilizumab (324 mg), according to drug availability. In addition, all patients but 1 received an additional dose of the drug within 24 hours. The mortality rate was 11%, and there was no statistically significant difference between subcutaneous and intravenous administration. At admission, 25 patients had a fever, which resolved in 24 patients within 24 hours of the treatment. Furthermore, PaO_2/FiO_2 (mm Hg) improved during the follow-up period (baseline, 152 ± 53; day 7, 283.73 ± 115.9; day 14, 302.2 ± 126; $P < .05$). Also, the CRP, ferritin, and D-dimer levels and lymphocyte count improved; however, no significant change in LDH levels was observed. Notably, the mean baseline D-dimer level was a predictor of death (HR, 5.01; 95%CI, 1.04-29.17). Finally, results showed that tocilizumab decreased the chance of mortality within 6 days of treatment (HR, 2.2; 95%CI, 1.3-6.7; $P < .05$).[70] A prospective single-center case series was carried out in 100 patients with severe COVID-19. Median age of patients was 62 years, with a male majority of 82%. The severity of respiratory disease was evaluated using the Brescia COVID-19 Respiratory Severity Scale (BCRSS).[71] This system classifies the severity of patients according to the need for ventilator support and oxygen supplementation, providing a step-up therapeutic approach for anti-inflammatory and antiviral drug use. Baseline comorbidities of patients were hypertension (46%), obesity (31%), diabetes mellitus (17%), and cardiovascular disease (16%). Patients with neutropenia (<500/mm^3), thrombocytopenia (<50,000/mm^3), suspected or confirmed bacterial infection, or active diverticulitis or gastrointestinal tract perforation were excluded. Patients received intravenous tocilizumab

(8 mg/kg) twice up to a maximum dose of 800 mg, with a 12-hour interval. A third dose was optional according to the clinical response after 24 hours of the second dose. Finally, 87% and 13% of patients received 2 and 3 doses of tocilizumab, respectively. Also, all the patients received a standard pharmacological protocol (antiviral drugs, antibiotic prophylaxis, hydroxychloroquine 400 mg/day, and dexamethasone 20 mg/day). Fifty-seven patients were treated with noninvasive ventilation (BCRSS = 3) in the general ward, of whom 63% died, 12% remained stable, and 23% worsened. Forty-three patients were treated in the ICU after tracheal intubation and mechanical ventilation (BCRSS > 3), of whom 74% improved, 2% remained stable, and 24% died. The clinical condition was improved or stabilized in 77% of patients, and 23% worsened. Finally, 20% of patients died. Also, lymphocyte count and CRP, fibrinogen, and ferritin levels improved within 10 days after treatment, whereas IL-6 and D-dimer levels increased. Serum levels of CRP dropped from 113 mg/L (45-169 mg/L) to 2 mg/L (1-5 mg/L), whereas serum levels (median [1st quartile to 3rd qquartile) of IL-6 increased from 41 pg/mL (10-102 pg/mL) to 1812 pg/mL (375-2600 pg/mL).[71] Furthermore, a retrospective study was done in 171 non-critically ill COVID-19 patients. Patients received the standard protocol including antiviral drugs, hydroxychloroquine, azithromycin, low-molecular-weight heparin (in patients with risk factors for thrombosis), and methylprednisolone (in patients with disease progression to ARDS). Among 171 patients, 77 were given tocilizumab, and 94 were not. Indeed, patients with progressive respiratory failure, and lymphocyte count $< 800/mm^3$, CRP $\geq$ 80 mg/L, or ferritin $\geq$ 800 mg/L were prescribed tocilizumab. The dose of tocilizumab was 400 mg for patients with $\leq$75 kg and 600 mg for patients with >75 kg. Patients with a partial response received 1 or 2 additional administrations every 12 hours. Comparing outcomes of the groups revealed that patients in the tocilizumab group had significantly fewer ICU admissions and the need for invasive ventilation, compared with the control group (10.3% vs 27.6%, $P = .005$; 0% vs 13.8%, $P = .001$). Also, the mortality rate (10.3%) was lower in patients receiving tocilizumab compared with other reports. Importantly, according to multivariable analyses (considering potential confounders), tocilizumab remained a strong protective variable of ICU admission or death (OR, 0.03; 95%CI, 0.007-0.1; $P = .0001$). Indeed, this nonrandomized clinical trial showed the beneficial effects of tocilizumab (400 or 600 mg) administration in the early stages of an inflammatory storm. It is important to mention that clinical deterioration of COVID-19 and the development of ARDS is rapid, and timely identification and treatment are vital. Patients should be evaluated regarding the factors that predict the progression of the disease to complicated stages.[72] A systematic review and meta-analysis of 30 studies including 53 000 COVID-19-confirmed patients showed that the risk factors for prediction of poor prognosis of early-stage patients are: old age, male sex, presence of comorbidities including chronic kidney disease, chronic obstructive pulmonary disease, cancer, hypertension, and diabetes, and laboratory indicators such as lymphopenia, thrombocytopenia, and elevated D-dimer, CRP, low-density lipoprotein, alanine aminotransferase (ALT), creatine kinase, and mainly IL-6 levels. Screening for hyperinflation as well as the prognostic factors identifying the severity of the disease is recommended for all patients with COVID-19.[73]

Numerous ongoing studies are being carried out to evaluate the efficacy and safety of tocilizumab in patients with COVID-19 (Table 2). Among these 24 studies, 12 are based in Europe, 10 in China, and 2 in the United States. Study sample size ranges from 20 to 500, with a cumulative sample size of 4269. Eligibility criteria vary across studies. Several factors such as severity of the disease, respiratory status, risk factors for progression, and levels of cytokines were considered. The route of administration was subcutaneous or intravenous. Dosage of tocilizumab was based on patient weight and/or a fixed dose ranging from 1 to 8 mg/kg and/or 80 to 800 mg in each administration. Considering clinical response and trial protocol, patients could receive 1 or 2 additional administrations of the medicine with intervals of 12 to 48 hours in some trials. The most common dosage was intravenous tocilizumab (8 mg/kg) up to 800 mg, which is similar to the FDA-approved dose for CAR T-cell therapy-induced CRS. The studies compare tocilizumab with usual care or other agents with a possible beneficial effect in COVID-19. Finally, there was significant heterogeneity in the primary end points of studies, such as mortality rate, resolution of fever at 24 hours, clinical improvement, biochemical response, oxygen saturation, need for mechanical ventilation, and change in Sequential Organ Failure Assessment (SOFA) score.

Based on China's National Health Commission recommendation, tocilizumab should be considered for the treatment of patients infected with COVID-19 with elevated IL-6 levels and serious lung damage.[74] The FDA has approved a randomized, double-blind, placebo-controlled phase 3 trial called a study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA) to evaluate the efficacy and safety of intravenous tocilizumab 8 mg/kg (up to the maximum of 800 mg per dose) in patients with COVID-19 pneumonia. In this study, patients were allowed to receive an additional dose based on their clinical condition. The inclusion

Table 2. Summary of Ongoing Clinical Trials Investigating the Therapeutic Effect of Tocilizumab for the Treatment of COVID-19

ID	Status	Design	Country	Population (Number of Patients)	Intervention Group(s)	Comparison Group(s)	Primary Outcomes
NCT04317092	Recruiting	Multicenter single-arm, open-label clinical trial	Italy	COVID-19 pneumonia (400)	Tocilizumab 8 mg/kg (up to 800 mg per dose) IV, with an interval of 12 hours.	No comparison group	One-month mortality rate
NCT04345445	Not recruiting	Open-label, randomized, crossover clinical trial	Malaysia	COVID-19 (310)	Tocilizumab 8 mg/kg IV once.	Methylprednisolone 120 mg/day for 3 days	Requiring mechanical ventilation, mean days of ventilation
NCT04331795	Recruiting	Single-group clinical trial	United States	Hospitalized, non–critically ill patients with COVID-19 pneumonia (50)	Tocilizumab low-dose 80 or 200 mg IV (based on risk factors for decompensation) up to 2 doses within 24 hours based on response.	No comparison group	Clinical response, biochemical response
NCT04332094	Recruiting	Randomized, multicenter, open-label clinical trial	Spain	COVID-19 (276)	Hydroxychloroquine plus azithromycin plus tocilizumab 162 mg SC × 2 doses plus tocilizumab 162 mg SC × 2 doses at 12 hours (day 1).	Hydroxychloroquine plus azithromycin	In-hospital mortality, need for mechanical ventilation in intensive care
NCT04346355	Recruiting	Open-label, randomized multicenter clinical trial	Italy	COVID-19 pneumonia (398)	Standard care plus tocilizumab 8 mg/kg IV up to a maximum of 800 mg with repetition of the same dosage after 12 hours.	Standard of care	Entry into intensive care with invasive mechanical ventilation or death
NCT04335071	Not recruiting	Multicenter double-blind, randomized, controlled clinical trial	Switzerland	SARS-CoV-2 infection (100)	Tocilizumab 8 mg/kg IV after confirmation of progressive dyspnea. Repeated once if no improvement in the 8-point WHO scale.	100 mL of NaCl 0.9% after confirmation of progressive dyspnea	ICU admission or intubation or death
NCT04320615	Recruiting	Randomized, double-blind, placebo-controlled multicenter	United States	Severe COVID-19 pneumonia (330)	Tocilizumab 8 mg/kg IV; an additional dose may be given if clinical symptoms worsen or show no improvement.	Placebo	Clinical status assessed using a 7-category ordinal scale
NCT04332913	Recruiting	Observational	Italy	COVID-19 respiratory distress syndrome and cytokine-release syndrome (30)	Tocilizumab 400 mg IV in a single dose, with a possible second dose in case of no clinical response.	No comparison group	Complete recovery defined as fever disappearance and return to normal peripheral oxygen saturation values
NCT04306705	Recruiting	Observational	China	COVID-19 cytokine-release syndrome (120)	Tocilizumab 8 mg/kg IV once in 100 mL of 0.9% saline IV.	Continuous renal replacement therapy	Normalization of fever and oxygen saturation
NCT04310228	Recruiting	Three-arm, multicenter, randomized, controlled trial	China	COVID-19 (150)	Tocilizumab 4 to 8 mg/kg IV once; an additional dose may be given if there is fever after 12 hours alone or with favipiravir.	Favipiravir alone	Clinical cure (viral negative load, lung image improvement, clinical manifestation)

(*Continued*)

Table 2. Continued

ID	Status	Design	Country	Population (Number of Patients)	Intervention Group(s)	Comparison Group(s)	Primary Outcomes
NCT04331808	Not recruiting	Multiple randomized, controlled trials	France	Moderate or severe COVID-19 pneumonia (240)	Tocilizumab 8 mg/kg. If no response (no decrease of oxygen requirement), a second injection after 2 days.	Standard care	Survival without needs of ventilator utilization, WHO progression scale $\leq$ 5, cumulative incidence of successful tracheal extubation
NCT04322773	Recruiting	Randomized, factorial-designed clinical trial	Belgium	COVID-19 acute hypoxic respiratory failure and systemic cytokine release syndrome (342)	Tocilizumab (400 mg), IV tocilizumab, (2 $\times$ 162 mg), SC sarilumab (200 mg), SC.	Usual care	Time to clinical improvement
NCT04315480	Active, not recruiting	Single-group clinical trial	Italy	COVID-19 severe pneumonitis (38)	Tocilizumab 8 mg/kg single intravenous administration.	No comparison group	Arrest in deterioration of pulmonary function, improving in pulmonary function
NCT04333914	Recruiting	Controlled, randomized, multicenter clinical trial	France	Advanced or metastatic cancer and COVID-19 infection (273)	Chloroquine analog nivolumab tocilizumab 400 mg.	Standard care	28-day survival rate
NCT04339712	Recruiting	Factorial assignment	Greece	(COVID-19) associated with organ dysfunction (20)	In case of diagnosis of MAS, IV anakinra 200 mg. In case of diagnosis of immune dysregulation, tocilizumab 8 mg/kg once up to a max of 800 mg.	No comparison group	Change of SOFA score, improvement of lung involvement measurements, Increase of pO_2/FiO_2 ratio
NCT04335305	Recruiting	Multicenter randomized, controlled, open-label phase 2 clinical trial	Spain	COVID-19-related mild acute respiratory syndrome nonresponsive to frontline therapy (24)	Tocilizumab 8 mg/kg, an additional dose based on respiratory function after 12 hours plus pembrolizumab.	Standard care	Normalization of SpO_2 $\geq$ 96%
IRCT2020040604 6968N1	Recruiting	Clinical trial	Iran	COVID-19 with P/F $<$ 300 negative IGRA test IL-6 $>$ 7 (100)	Tocilizumab 400 mg IV plus standard care.	Standard care	Oxygenation status, complications in vital organs, hemodynamic disturbances, duration of mechanical ventilation, mortality
IRCT20151227025726N13	Recruiting	Noncontrolled clinical trial	Iran	COVID-19 with respiratory rate $>$ 30/min oxygen saturation $<$ 90%, PaO_2/FiO_2 $<$ 300 mm Hg, high level of IL-6 (40)	Hydroxychloroquine plus oseltamivir 75 plus lopinavir-ritonavir plus tocilizumab 400-mg IV infusion as a single dose.	No comparison group	Fever, cough, dyspnea

(*Continued*)

Table 2. Continued

ID	Status	Design	Country	Population (Number of Patients)	Intervention Group(s)	Comparison Group(s)	Primary Outcomes
IRCT20150303021315N17	Recruiting	Phase 3 open-label and single-arm study	Iran	COVID-19 with $SpO_2 \leq 93\%$, high IL-6 (500)	Conventional therapy plus tocilizumab (4-8 mg/kg) IV or (2 or 3 injections of 162 mg plus the standard treatment. Inadequate response: administered with a 12-hour interval between injections.	No comparison group	Normalization of fever and oxygen saturation within 14 days of treatment
ChiCTR2000029765	Recruiting	Multicenter randomized, controlled trial	China	COVID-19 pneumonia with high IL-6 (188)	Conventional therapy plus tocilizumab.	Conventional therapy	Cure rate
ChiCTR2000030196	Not yet recruiting	Multicenter nonrandomized, open-label intervention	China	Severe COVID-19 pneumonia with high IL-6 and grades 2-3 cytokine-release syndrome (60)	Tocilizumab plus conventional therapy.	No comparison group	Resolution of cytokine-release syndrome
ChiCTR2000030442	Canceled by investigator	Single-center nonrandomized intervention	China	Severe COVID-19 pneumonia (100)	Tocilizumab, IV immunoglobulin, and CRRT.	No comparison group	Duration of hospitalization
ChiCTR2000030894	Recruiting	Multicenter randomized, controlled trial	China	COVID-19 pneumonia (150)	Favipiravir combined with tocilizumab 4-8 mg/kg. For fever patients, an additional application is given if there is still fever within 24 hours, the interval between 2 medications $\geq$ 12 hours.	No comparison group	Clinical cure rate
NCT04359667	Recruiting	Prospective single-center study	Croatia	Severe pneumonia (30)	Tocilizumab (1-8 mg/kg) up to 800 mg per dose can be repeated once after 12 hours plus standard treatment.	No comparison group	IL-6 and sIL-6R levels during 28 days

COVID-19, coronavirus disease 2019; IV, intravenous; SC, subcutaneous; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; WHO, World Health Organization; MAS, macrophage activation syndrome; SOFA, sequential organ failure assessment, PaO_2/FiO_2, atrial partial pressure of oxygen/fraction of inspiration O_2; IGRA, Interferon Gamma Release Assay; IL, interleukin; CRRT, continuous renal replacement therapy; sIL-6R, soluble interleukin-6 receptor.

criteria were hospitalized patients with COVID-19 pneumonia according to WHO criteria, chest x-ray, or CT scan.[75] Moreover, the Italian Regulatory Agency has approved a multicenter study (TOCIVD-19) to evaluate the efficacy and safety of tocilizumab 8 mg/kg (up to a maximum of 800 mg per dose) in the treatment of COVID-19 pneumonia patients. Patients can receive a second administration (same dose) after 12 hours. Notably, the study project includes a parallel observational cohort study and a single-arm phase 2 study. The inclusion criteria were confirmed diagnosis of SARS-CoV-2 infection and oxygen saturation $\leq$ 93% in ambient air. In addition, patients with intubation less than 24 hours before registration are enrolled in phase 2 and those with intubation more than 24 hours before registration in an observational cohort. Patients are evaluated regarding laboratory data (blood count, bilirubin, aspartate aminotransferase [AST], ALT, creatinine, prothrombin time, partial thromboplastin time, LDH, D-dimer), atrial blood pressure, 12-lead electrocardiogram, vital signs, SOFA score, radiologic findings, and use of respiratory assistance during the sutdy period. One-month mortality rate is the primary end point of the study. The secondary end points of the

study include duration of hospitalization, evaluation of CRP and IL-6 levels in correlation with treatment outcomes, respiratory symptoms, time to invasive mechanical ventilation, definitive extubation, independence from oxygen therapy, radiological response, trends of PaO_2/FiO_2 ratio, SOFA score, and lymphocyte count, and tocilizumab toxicity. The Italian guideline recommended the presence of at least 1 of the following criteria before tocilizumab administration: IL-6 level > 40 pg/mL (or D-dimer > 1000 mg/L), PaO_2/FiO_2 ratio < 300 mm Hg, respiratory gas exchange rapidly worsening. According to the University of Michigan recommendations, tocilizumab should be considered in COVID-19 patients with abnormalities in chest imaging, rapid worsening of gas exchange requiring >6 L/min O_2, laboratory parameters of CRS, need for supplemental O_2 to maintain PaO_2/FiO_2 < 300 mm Hg or oxygen saturation < 92%, and at least 2 laboratory abnormalities (lymphocyte count < 600/mm^3, D-dimer > 1000 mg/L, ferritin > 500 mg/L, LDH > 250 units/L, or CRP > 100 mg/L or > 50 mg/L the past 48 hours).[76,77]

Because immune system antiviral activity is vital to recovering from SARS-CoV-2 infection, the pros and cons of using tocilizumab on these patients should be considered with caution. Based on animal studies, IL-6 plays an important role in the clearance of viruses as well as control of pulmonary inflammation. Clinicians should consider the severity of the viral load or replication status and hyperinflammation. The application of some tools to design the severity scale of COVID-19 focusing on CRP and IL-6 levels, ferritin, platelet count, leukocyte count, erythrocyte count, and sedimentation rate is useful to guide clinicians in starting treatment. Furthermore, the application of the Histological Score (HScore) has been recommended to recognize COVID-19 patients at high risk for hyperinflammation. The HScore is used for the evaluation of secondary hemophagocytic lymphohistiocytosis considering laboratory and clinical parameters, including body temperature, organomegaly, hemophagocytosis on bone marrow aspirate, signs of immunosuppression, and serum AST, triglycerides, fibrinogen, cytopenias, and ferritin. Also, patients should be evaluated considering clinical manifestation and laboratory findings of CRS. As discussed earlier, the administration of tocilizumab as a selective immunosuppressive drug instead of broad immunosuppressive drugs is recommended to avoid the suppression of the antiviral activity of the immune system. Furthermore, the timing of treatment is important to decrease the adverse effects of tocilizumab; however, evidence regarding the proper timing of administration is not definitive. In addition, the true dose of tocilizumab is currently unknown and needs to be addressed by studies that are underway. More research is needed to determine when and for which patients, tocilizumab should be administered.[78,79] Based on recent data, tocilizumab can be considered in patients with extensive lung involvement and severe or critical patients with high IL-6 levels. Intravenous tocilizumab should be diluted to 100 mL with 0.9% normal saline, and the infusion time is at least 1 hour. The maximum dose should not exceed 800 mg intravenously. If clinical improvement does not take place after the first dose, 1 additional dose may be considered within at least 12 hours; however, up to 2 additional doses have been used in some studies. The recommended dose of tocilizumab in CAR-T-cell therapy-induced CRS is 8 mg/kg (>30 kg) and 12 mg/kg (<30 kg) up to 800 mg in each administration) intravenously with at least an 8-hour interval up to 4 doses. In the study by Moreno-García et al,[72] 1 to 3 administrations of lower doses of tocilizumab (400 or 600 mg) in the early stages of COVID-19-induced cytokine storm showed beneficial effects in decreasing ICU admissions and death. Consequently, recognizing patients with risk factors for disease progression is useful. Importantly, in similar clinical conditions such as CAR-T-cell and BiTE therapy-induced CRS, subcutaneous tocilizumab has not been recommended. As well, in chronic conditions such as RA, the maximum dose of subcutaneous tocilizumab is 162 mg. Notably, in the prospective case series by Sciascia et al,[70] patients were given subcutaneous (324 mg) or intravenous (8 mg/kg) tocilizumab in COVID-19-induced CRS, and the difference in mortality rate was not statistically significant between these 2 routes of drug administration. Taken together, based on limited data, tocilizumab is effective for patients with severe and critical COVID-19-related ARDS and needs to be addressed by ongoing clinical trials.

Tocilizumab Safety and Potential for Toxicity

Adverse reactions to chronic administration of tocilizumab have been assessed in patients with rheumatologic diseases such as RA and GCA. In a double-blind, randomized, placebo-controlled, parallel-group phase 3 study, 623 patients with RA were randomized to intravenously receive tocilizumab 8 mg/kg (n = 205), tocilizumab 4 mg/kg (214), or placebo (204) every 4 weeks, with fixed doses of methotrexate. The results showed serious infection, the most common serious adverse event, were observed in 6, 3, and 2 patients, respectively.[80]

The tocilizumab safety data were collected from 5 core phase 3 trials, 2 ongoing extension trials, and 1 clinical pharmacology study. A total of 4199 included patients were categorized based on tocilizumab

administration and dose as follows: tocilizumab 8 mg/kg (n = 1870), tocilizumab 4 mg/kg, and patients with no tocilizumab administration (n = 1555). The most common adverse event and severe adverse event were infection. The rate of infection was 112.7/100 patient-years (PY) in the tocilizumab 8-mg/kg group, 115.7/100 PY in the tocilizumab 4-mg/kg group, and 105.8/100 PY in the control group. The rate of severe adverse events was similar in the 3 groups (tocilizumab 8 mg/kg, 14.5/100 PY; tocilizumab 4 mg/kg, 13.6/100 PY; control, 14.4/100 PY). The rate of overall adverse events was 381.6/100 PY in the tocilizumab 8-mg/kg group, 358.0/100 PY in the tocilizumab 4-mg/kg group, and 339.0/100 PY in the control group.[81] A meta-analysis of 6 initial trials and 5 long-term extensions in 601 Japanese patients, with 2188 PY exposure was carried out to evaluate efficacy and safety of tocilizumab monotherapy in patients with moderate to severe rheumatoid arthritis. The result showed the incidence of adverse events was 465.1 per 100 PY. Furthermore, mild abnormality in lipid profile or liver function tests was common; however, none of them were categorized as severe adverse events. In addition, the most common serious adverse event was infection (6.22 per 100 PY).[82] A systematic review and network meta-analysis of 11 randomized, controlled trials and 8 cohort studies showed good cardiovascular safety of tocilizumab compared with other biological disease-modifying antirheumatic drugs in patients with RA. Moreover, it has been indicated that tocilizumab has potential benefit on myocardial infarction compared with other biological disease-modifying antirheumatic drugs.[83]

The common adverse reactions of tocilizumab include infection, increased serum cholesterol, ALT, and AST, and injection-site reaction. Understanding tocilizumab safety and potential for toxicity in other diseases could guide clinicians in determining potential exclusion criteria in COVID-19 treatment. Tocilizumab contraindications include known hypersensitivity to tocilizumab and active infection (including localized infection). Notably, herpes zoster reactivation has been reported. Importantly, reactivation of latent tuberculosis and new infections have been observed. Before tocilizumab administration, patients should be tested concerning latent tuberculosis. In addition, it should be used with caution in patients with high risk for gastrointestinal perforation, neutropenia (absolute neutrophil count [ANC] < 2000/mm^3: do not initiate; ANC < 500/mm^3: discontinue), thrombocytopenia (platelet count < 100 000/mm^3: do not initiate treatment; platelet count < 50 000/mm3: discontinue treatment), hepatic impairment, demyelinating disorders, and hyperlipidemia.[81-84] Notably, patients with neutropenia (<500/mm^3), thrombocytopenia (<50 000/mm^3), suspected or confirmed bacterial infection, or active diverticulitis or gastrointestinal tract perforation were excluded from the Toniati et al study.[71] To date, the published studies have not reported most of them as exclusion criteria; however, exclusion criteria of the COVACTA trial are as: patients with known severe allergic reactions to tocilizumab or other monoclonal antibodies, active tuberculosis infection, suspected active infection other than COVID-19, receiving other immunomodulatory drugs within the past 3 months, pregnancy, lactation, platelet count < 50 000/mm^3, ANC < 1000/mm^3, ALT or AST > 10 times the upper limit of normal, and participating in other drug clinical trials within 30 days or 5 half-lives of the investigational drug. Notably, according to the Massachusetts General Hospital COVID-19 treatment guidelines, patients with suspected tuberculosis, including foreign-born patients from resource-limited countries and patients with homelessness should be tested before tocilizumab administration. Moreover, suspected patients for strongyloides should be treated empirically with ivermectin if receiving tocilizumab. Furthermore, IL-6 serum level should be measured before tocilizumab administration. In addition, the Italian guidelines recommended measurement of CRP, D-dimer, and ferritin with or without IL-6 level before and after each administration. Finally, exclusion criteria include hypersensitivity to tocilizumab or its excipients, concomitant immunomodulators or antirejection drugs, active infections, platelets < 50 000/mm^3, neutrophils < 500 /mm^3, ALT or AST > 5 times the upper limit of normal, bowel diverticulitis or perforation, and other contraindications of tocilizumab.[75-77]

It is important to mention that IL-6 elevation is not an accurate indicator to reflect its functional downstream effects. CRP as a marker of IL-6 bioactivity is synthesized through IL-6-dependent hepatic biosynthesis.[82] Tocilizumab administration increases the serum levels of soluble IL-6 receptor because eof the longer elimination half-life of tocilizumab with soluble IL-6 receptor immune complex compared with the soluble IL-6 receptor. In addition, IL-6 level increases after tocilizumab administration through inhibition of IL-6 consumption. Importantly, it has been indicated that the administration of tocilizumab does not increase the production of IL-6. According to the published data in COVID-19, regardless of clinical outcome, the administration of tocilizumab is associated with CRP serum level reduction. Conversely, after the administration of tocilizumab, a mild increase in IL-6 serum level was observed in all patients, followed by a dramatic increase in patients with disease aggravation or mortality (Table 3).

The disease-related conditions in COVID-19, the clinical condition of the patient, and treatment duration may influence the incidence of adverse events.

Table 3. CRP and IL-6 Levels in Published Clinical Trials Investigating the Therapeutic Effect of Tocilizumab for the Treatment of COVID-19

Author, Year, Sample Size	IL-6 Follow-up (Days)	IL-6 Before Therapy (pg/mL), Mean ± SEM	IL-6 After Therapy (pg/mL), Mean ± SEM	IL-6 Changes (pg/mL), Mean ± SEM	CRP Follow-up (Days)	CRP Before Therapy (mg/L), Mean ± SD	CRP After Therapy (mg/L), Mean ± SD	CRP Changes (mg/L), Mean ± SEM
Xu et al (2020), 21	NA	NA	NA	NA	5 (5-5)	75.1 ± 14.5	2.7 ± 0.7	−72.3 ± 13.8
Luo et al (2020), 15	7 (3-7)	111.0 ± 43.8	1228.0 ± 470.3	1117 ± 426.5	7 (4-7)	131.8 ± 19.9	16.8 ± 6.9	−115 ± 13
Sciascia et al (2020), 63	14 (6-14)	105 ± 15	1125 ± 245	1150 ± 230	14 (6-14)	135 ± 15	13 ± 3	−123 ± 12
Toniati et al (2020), 100	10[a]	41 (10-102)[b]	1812 (375-2600)	1771 (365-2498)	10	113 (45-169)	2 (1-5)	−111 (44-164)

IL, interleukin; CRP, C-reactive protein; SD, standard deviation.
Follow-up days present as median (range) and have been estimated from Sciascia et al results. IL-6, and CRP values have been estimated from Figures 1 and 2 in Sciascia et al.
[a]Follow-up days range was not available for Toniati et al.
[b]IL-6 and CRP serum levels data have been expressed as median (1st quartile-3rd quartile).

A retrospective analysis of patients with CAR T-cell-induced CRS showed no adverse events with tocilizumab, suggesting its safety in both adults and pediatric patients.[84] Notably, tocilizumab adverse events were assessed in patients with different demographic and clinical characteristics. As an example, patients in CAR T-cell-induced CRS trials were younger than those with severe COVID-19. To date, no well-designed clinical trial has been published regarding tocilizumab safety in patients with COVID-19. In the case series by Toniati and colleagues, 3 severe adverse events were observed during the 10-day follow-up. Among them, 2 patients died ecause of septic shock, and 1 experienced gastrointestinal perforation. In the study by Sciascia et al, the safety of tocilizumab was evaluated as the primary end point in patients with severe COVID-19, and no moderate to severe adverse events related to the drug were reported. Also, no adverse reactions were reported in other studies.[67,69-72] Finally, drug interactions of tocilizumab should be considered. It may enhance the effects of other immunosuppressants. Importantly, tocilizumab is a cytochrome P450 enzyme inducer and may decrease the serum concentration of cytochrome P450 3A4 substrates. Consequently, it is recommended that rivaroxaban and apixaban should not be used in those receiving tocilizumab. In addition, dose adjustments of warfarin are also recommended in these patients. Notably, warfarin is primarily metabolized via cytochrome P450 2C9. The proposed mechanism of action of drug interactions is the effect on decreasing the effect of IL-6 and thus upregulation of transporters and drug metabolism enzymes.[85-91] Taken together, according to the limited data, administration 1 or 2 times of both intravenous and subcutaneous tocilizumab in the mentioned doses is considered safe in patients with severe/critical COVID-19; however, the tocilizumab safety data for other conditions should be considered in determining exclusion criteria in future clinical trials and practice.

Limitations

This review may have some limitations. First, the treatment of COVID-19 is fluid with the discovery of new knowledge about disease-modifying treatment plans. Next, we reference some documents in preprint status that had not been peer reviewed at the time of writing this article. So, caution should be used in referencing these documents until publication.

Conclusion

To date, data about the use of tocilizumab in the treatment of acute lung injury in patients with COVID-19 are not adequate to draw a conclusion. More large and well-designed randomized clinical trials are still

needed to confirm the efficacy and safety of tocilizumab in patients with COVID-19 developed ARDS. As well, future studies are recommended to provide a score for determining the indication for tocilizumab based on disease severity, burden of lung injury, presence of risk factors, and levels of inflammatory markers, importantly IL-6. It would help clinicians to find out which population benefits more from the drug. At this time because of a lack of data, until the determination of results of ongoing clinical trials, clinical considerations about the use of tocilizumab in patients with COVID-19 should be taken in terms of patient selection, treatment dose, combination with other therapies, and safety issues.

Conflicts of Interest

The authors have nothing to disclose.

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