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The Role of Interleukin-6 in the Pathogenesis, and Treatment of SARS-CoV-2

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is life-threatening pneumonia caused by an enveloped, single-stranded RNA betacoronavirus belonging to the corona viridae family. Pathophysiologically, SARS-CoV-2 is due to the severe hyperinflammatory host response to the coronavirus, resulting in overproduction of cytokines, chemokines, and growth factors by macrophages, such as interleukin-1β (IL-1β), IL-2, IL-6, IL-8, tumor necrosis factor-a. SARS-CoV-2 is characterized by diffuse alveolar damage due to direct infection of alveolar type II pneumocytes, pulmonary oedema, vascular occlusion, ventilation/perfusion mismatch, and interstitial infiltrates, which rapidly progress to hypoxemia, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. The standard of care of Covid-19 includes high-flow nasal oxygen (HFNO), dexamethasone, remdesivir, and invasive mechanical ventilation IMV) or extracorporeal membrane oxygenation in very severe cases.

However, mortality is exceptionally high even with these therapies. IL-6 plays a key role in orchestrating the cytokine storm, and hyper inflammation characteristics of Covid-19, leading to respiratory failure, and multi-organ failure. Interleukin-6 signaling is via the IL-6 receptor (IL-6Ra), which exists in two isoforms, transmembrane IL-6Ra, and soluble IL-6Ra. Two IL-6Ra antagonists have been issued an emergency use authorization by the FDA, including tocilizumab, and sarilumab. Interleukin-6 receptor antagonists are safe, and effective in the treatment of severe Covid-19, particularly in patients requiring HFNO, or respiratory support. Tocilizumab is the most studied IL-6Ra antagonist in the treatment of severely ill patients with Covid-19. Tocilizumab co-administered with dexamethasone is superior to the standard of care alone in the treatment of hypoxemic patients requiring IMV. The duet has been shown to reduce the need for mechanical ventilation and to reduce the mortality in critically ill patients with Covid-19.

***Keywords**: Covid-19, Cytokine storm, Dexamethasone, Interleukin-6, Tocilizumab.*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is life-threatening pneumonia caused by an enveloped, single-stranded RNA betacoronavirus belonging to the corona viridae family [1], which initially originated from Wuhan, Hubei province, China [2]. SARS-CoV-2 five waves of pandemics have infected 160 million people worldwide, and have caused the death of about 3.5 million individuals as of June 17, 2021, globally [3]. Covid-19 pandemics have had devastating public health, socio-economical, commercial, and industrial consequences, due to lock-downs in many countries.

Approximately 80% of the patients with COVID-19 disease develop a mild illness, whereas 15-30% progress to critical disease with respiratory failure, and multi-organ failure (MOF) [4].

SARS-CoV-2 is characterized by the severe hyperinflammatory host response to the coronavirus, resulting in overproduction of cytokines, chemokines, and growth factors by macrophages (cytokine storm), such as IL-1β, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, tumor necrosis factor-α (TNF-α), GM-CSF, and interferon-γ (IFN-γ) [5-8]. Several other cytokines, chemokines, and growth factors are secreted by the activated immune, inflammatory, and structural cells during the cytokine storm due to coronavirus 2 systemic infection [9-12]. Table 1 shows the myriad of inflammatory mediators secreted by inflammatory, and immune cells during the cytokine storm due to Covid-19 infection.

The cytokine storm is a type of hyper inflammation, whereby there is excessive production of proinflammatory cytokines in a dysregulated manner in response to infection, trauma, and chimeric

antigen receptor T-cell (CAT-T) therapy [9-12]. Overproduction of IL-1β, IL-6, IL-8, and TNF-α, in particular, is associated with severe Covid-19 disease, and very poor prognosis [13]. Recently, Cruz et al. [14] have reported that high levels of serum IL-6 are associated with fatal severe SARS-CoV-2 pneumonia.

Table 1. Inflammatory cytokines, chemokines, and growth factors secreted during the cytokine storm, and SARS-CoV-2

Cytokines	Chemokines
Interleukin-1β (IL-1β	Macrophage inflammatory protein-1 (MIP-1α/CCL3)
IL-1RA	Monocyte chemoattractant protein-1 (MCP-1/CCL2)
IL-2	Interferon gamma-induced protein 10 (IP-10/CXCL10)
IL-6	Growth factors
IL-8 (CXCL8)	Granulocyte colony-stimulating factor (G-CSF)
IL-9	Granulocyte-macrophage colony stimulating factor (GM-CSF)
IL-10	Fibroblast growth factor (FGF)
IL-17	Tumor necrosis factor –α (TNF-α)
IL-18	Interferon-gamma (IFN-γ)

Table 2. Immune and structural cells which secrete cytokines, and chemokines responsible for the cytokine storm

Inflammatory and immune cells	**Structural cells**
Macrophages	Epithelial cells
Monocytes	Endothelial cells
Mast cells	Astrocytes
Neutrophils	Microglia
Dendritic cells	Neurons

CD4+ Th2 lymphocytes	Adipocytes
B cells	Malignant cells
Natural killer T cells	

Table 3. Anti-viral agents in clinical trials for the treatment of SARS-CoV-2

Antiviral	**FDA Status**
Remdesivir	Approved 2020
Favipiravir	NA
Ribavirin	NA
Lopinavir	NA
Lopinavir plus ritonavir	Recommended, approved for AIDS in 2000
Ritonair	EUA 2021
Darunavir	NA
Umifenovir (Arbidol)	NA
Molnupiravir	EUA 2021
Nirmatrelvir plus ritonavir	EUA 2021

Abbreviations: EUA, Emergency Use Authorization; FDA, Food and Drug Administration; NA, Not approved; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2. The FDA status may change with time, and emerging clinical data.

Table 4. Monoclonal antibodies in clinical trials for the treatment of SARS-CoV-2

Monoclonal antibody	Target	Dosage	FDA status
Anakinra	IL-1α, IL-1β	200 mg, 100 mg Q6h	EUA 2021
Canakinumab	IL-1β	459-750 mg infusion	NA
Tocilizumab	IL-6Rα	8 mg/kg (Max 800 mg)	EUA 2021
Sarilumab	IL-6Rα	400 mg in 100 ml saline	NA
Baricitinib	JAK1, JAK2	1-4 mg PO OD x 14 days	EUA 2020
Tofacitinib	JAK1, JAK3	10 mg PO BD x 14 days	EUA 2021
Bamlanivimab	Spike protein	700 mg IV single dose	EUA 2021
Etesevimab	Spike protein	1.4 g IV single dose	EUA 2021
Casirivimab	Spike protein	600 mg IV OD	EUA 2021
Imdevimab	Spike protein	600 mg IV OD	EUA 2021
Sotrovimab	SARS-CoV-1/2 epitope	500 mg IV infusion	EUA 2021
Mavrilimumab	GM-CSFRα	6 mg/kg IV infusion	Phase 2/3

Abbreviations: BD, twice daily; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; GM-CSF, Granulocyte-macrophage colony stimulating factor; IV, Intravenous; JAK, Janus kinase; OD, Once daily.

Pathophysiology of SARS-CoV-2

SARS-CoV-2 infection primarily affects T lymphocytes, particularly CD4+ T, and CD8+ T cells, resulting in a decrease in their blood counts, and a reduction in the production of IFN-γ [12]. This is accompanied by the production of several cytokines, chemokines, and growth factors by macrophages, and other inflammatory cells, which are responsible for the cytokine storm, acute lung injury (ALI), and severe SARS-CoV-2 [7-9].

SARS-CoV-2 manifests as extensive lung damage, severe pneumonia, and hypoxemia, which may rapidly progress to acute respiratory distress syndrome (ARDS), multiorgan failure, and death, if not treated aggressively by the standard of care (SoC), and invasive mechanical ventilation [15,16]. The causes of

severe acute hypoxemia due to SARS-CoV-2 are multifactorial, such as diffuse alveolar damage (DAD) [17,18], pulmonary oedema, interstitial infiltration, development of hyaline membranes, hemoglobinopathies, endothelitis, vascular occlusion, ventilation-perfusion mismatch, and shunts [18,19]. Diffuse alveolar damage is due to direct infection of alveolar type II pneumocytes by SARS-CoV-2 [20].

Persistent hypoxaemia with SaO2 < 94%, and PaO2/FiO2 ratio < 300 mm Hg can lead to pulmonary hypertension, and hemodynamic compromise. Furthermore, coronavirus has a tropism for cardiomyocytes, and pericardial serosal cells, and can result in arrhythmias, myocarditis, pericarditis, cardiomyopathy, and heart failure [21,22].

The infected and damaged cells in the lung, including pneumocytes, bronchial epithelial cells, macrophages, and several immune cells undergo apoptosis and die leading to the production of excessive pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNF-α, and IFN-γ [5-8]. The inflammatory cytokines and chemokines are responsible for the cytokine storm, acute lung injury, ARDS, respiratory failure, and multi-organ failure [15,16].

Severe Covid-19 disease is associated with extrapulmonary organ damage, such as septic shock, acute cardiac injury, cardiomyopathy, heart failure [21,22], acute kidney injury, renal failure [23,24], acute liver injury [25], disseminated intravascular coagulation (DIC), thromboembolism [26], neurological disorders [27], and cerebrovascular disease [28,29].

Laboratory features of Covid-19 include raised white blood cell count, lymphopenia, thrombocytopenia, raised serum levels of C-reactive protein (CRP), procalcitonin, D-dimer, fibrinogen, ferritin [30,31], urea, creatinine [23,24], and transaminases [25]. Impaired liver function results in hypoalbuminemia, and high concentrations of total serum bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, and glutamyl transpeptidase [25].

Abnormal coagulation parameters include high serum levels of fibrinogen, and D-dimer are associated with poor prognosis in patients with novel coronavirus pneumonia, due to higher risk of thrombosis, particularly pulmonary embolism [32]. This is because; IL-6 stimulates the coagulation pathway leading to microthrombi in the pulmonary circulation, and increasing the risk of thrombotic events [33]. Thromboembolism can also occur in the cerebral vasculature, leading to stroke [29].

Interleukin-6 can induce hepatocytes to produce acute-phase proteins [34], such as CRP, serum amyloid A (SAA), fibrinogen, haptoglobin, and 1-antichymotrypsin. Increased serum levels of CRP, and D-dimer are associated with severe SARS-CoV-2, poor outcomes, and the need for non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV). CRP and D-dimer are useful biomarkers to depict the severity of Covid-19 and can guide therapy, and predict the prognosis in critically ill patients [14,32].

Interleukin-6 is a master player cytokine responsible for the cytokine storm [35]. Overproduction of IL-6, and dysregulation of the IL-6 signaling can result in inflammatory and autoimmune disorders [36], and even cancer [37,38]. Targeting IL-6, IL-6R, and the signaling kinases, such as Janus kinases (JAKs) is an attractive therapeutic approach to treat chronic inflammatory diseases, such as rheumatoid arthritis [36], and SARS-CoV-2 [39].

Interleukin-6

The interleukin-6 family cytokines is comprised of ten members, such as IL-6 [40], IL-11 [41], oncostatin M (OSM) [42], leukaemia inhibitory factor (LIF) [43], ciliary neurotrophic factor (CNTF) [44], and cardiotropin-1 (CT-1) [45]. Most of the IL-6 family members share a common membrane glycoprotein 130 kDa (gp130) co-receptor and a similar signal transducer subunit in their receptor complexes [46,47]. LIF, CNTF, CT-1, and corticotrophin-like cytokine (CLC) can also signal via LIF receptor (LIF-R), a protein structurally related to gp130 [48].

Interleukin-6 was discovered and cloned by Hirano and colleagues in 1986 [49]. Interleukin-6 is a small glycoprotein with a molecular mass of 21-28 kDa, comprising of 212 amino acids, including 28-amino acid signaling peptides. It is produced by inflammatory and immune cells such as macrophages, mast cells, neutrophils, dendritic cells, CD4+ Th2 lymphocytes, and B cells [50-53]. Additionally, IL-6 is secreted by structural cells, such as epithelial cells, endothelial cells, fibroblasts, adipocytes, astrocytes, neurons, and even malignant cells [53]. Table 2 shows the inflammatory, immune, and structural cells which secrete the cytokines, and chemokines responsible for the cytokine storm, including IL-6.

Several stressful stimuli are known to promote the production and secretion of IL-6, such as irradiation, ultraviolet light, reactive oxygen species (ROS), microbial products, viral infections, and pro-inflammatory cytokines, such as IL-1β, and TNF-α [54]. Currently, SARS-CoV-2 infection has emerged as a major inducer of the cytokine storm, which results in over-secretion of excessive IL-1β, IL-6, IL-8, and TNF-α.

Interleukin-6 Signaling

Interleukin-6 signaling is via the IL-6 receptor (IL-6Rα), which belongs to the immunoglobulin superfamily [55,56]. The IL-6 receptor exists as an 80 kDa transmembrane form (mIL-6Rα), and as a 50-55 kDa soluble form (sIL-6Rα), and both receptors are involved in IL-6 signaling [56]. Soluble IL-6Rα is produced by proteolytic cleavage of mIL-6Rα by a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) [57]. The gp130 protein which is essential for signaling is expressed in all the cells in the human body and acts as a signal-transducing co-receptor [58,59]. Signaling via mIL-

6R is called the classic pathway, whereas signaling through the sIL-6R is termed the trans-signaling [58].

In the classic pathway, IL-6 binds to membrane-bound IL-6 receptors (mIL-6Rα), and the complex of IL-6/mIL-6Rα associates with gp130, which dimerizes and initiates signaling [60]. The intracellular signaling is mediated by JAKs constitutively associated with the cytoplasmic portion of gp130 protein. This is followed by activation of the signal of transducers and activators of transcription (STATs), which after phosphorylation by Janus kinases dimerize and translocate into the nucleus. STATs (STAT1, and STAT3) act as transcription factors in the nucleus [61], and translate the biological, and immunopathophysiological effects of IL-6, such as the production of the cytokines responsible for hyperinflammation. The gp130 co-receptor mainly signals via JAK1, and STAT3 [62], but other IL-6 family members can signal via JAK1 and STAT1. Interleukin-6 can also signal via the JAK-MAPK (mitogen-activated protein kinase) pathway [63].

Interleukin-6 plays an important role in orchestrating the cytokine storm, and IL-6 activity correlates with the severity of SARS-CoV-2, the risk of requiring IMV, ECMO, and death. IL-6 is a pleiotropic cytokine implicated in several chronic inflammatory diseases, autoimmune disorders [36], and cancer [37,38]. IL-6 antagonists are currently very effective and are approved for the treatment of diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis, vasculitis, and recently SARS-CoV-2.

Treatment of SARS-CoV-2

There are no specific effective targeted antiviral agents for the treatment of Covid-19. Treatment of SARS-CoV-2 includes proper nursing care in a prone position, which has been documented to improve oxygen saturation (SaO2), and partial pressure of arterial oxygen (PaO2) [64,65]. High-flow nasal cannula oxygenation (HFNO) is the most recommended initial treatment of SARS-CoV-2. This can be delivered through a high-flow nasal cannula up to 60 L/min of nearly 100% oxygen [66]. The recommended target SaO2 is 92-96% in adults with severe Covid-19, using supplemental oxygen as needed [67].

Provision of low positive end-expiratory pressure (PEEP) of 2-5 cm H2O which does not induce alveolar over-distension is required for the effective delivery of oxygen, and in improving the PaO2 [68-70]. In patients with more severe hypoxemia due to pulmonary oedema, and atelectasis, the use of continuous positive airway pressure (CPAP) is recommended to increase the total lung capacity (TLC) by recruitment of collapsed lung units [70]. CPAP is usually delivered at pressure levels between 5 and 15 cm H2O [71-73]. Nevertheless, some of the patients with severe Covid-19 and multi-organ dysfunction may require non-invasive ventilation or invasive mechanical ventilation.

Corticosteroids

Corticosteroids (synonymous with glucocorticoids) are the most potent, and effective therapy for several chronic inflammatory diseases, and autoimmune disorders, such as rheumatoid arthritis, asthma, atopic dermatitis, inflammatory bowel disease (IBD), prevention of graft rejection, and most recently SARS-CoV-2. Corticosteroids have been used to treat severe acute lung injury due to hyper inflammation, such as acute respiratory distress syndrome (ARDS) due to Covid-19 with the rationale to downregulate or prevent hyper inflammation [74].

Several clinical trials have evaluated the efficacy and safety of corticosteroid therapy in critically ill patients with Covid-19. The most impressive results are from the RECOVERY trial which demonstrated that a moderate dose of dexamethasone (6 mg for 10 days) reduced mortality in hospitalized patients with Covid-19 and respiratory failure, who required therapy with supplemental oxygen or IMV [75]. In the dexamethasone group, the incidence of death was lower than in the usual care group patients receiving mechanical ventilation (29.3% versus 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81). In the patients receiving oxygen without mechanical ventilation the death rates were not very different (23.3% versus 26.2%); rate ratio, 0.82; 95%CI, 0.72 to 0.94). However, in the dexamethasone group in patients who were receiving no respiratory support at randomization, the death rates were slightly higher compared to the usual care (17.8% versus 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55) [75]. The results from the RECOVERY clinical trial indicate that moderate dose dexamethasone might increase mortality in hospitalized patients who were not receiving oxygen, and respiratory support [75]. Thus, dexamethasone is most beneficial in critically ill Covid-19 patients receiving HFNO, and NIV or IMV.

The positive outcomes from the RECOVERY study are supported by smaller clinical trials' findings, which also have documented the beneficial effects of dexamethasone, and hydrocortisone in reducing hospital mortality, and in preventing the need for IMV [76-82]. Tomazini et al. [76] have reported that intravenous dexamethasone in patients with severe Covid-19 led to a statistically significant in days alive, and free of mechanical ventilation over 28 days compared with standard of care (SoC) treatment alone.

Similarly, Villar et al. [83] have shown that high doses of dexamethasone for 10 days decreased overall mortality, and mechanical ventilation duration in patients with moderate-to-severe ARDS. This open-label, randomized, multicentre trial in 277 patients with moderate-to-severe non-COVID-19-related ARDS found a 15% absolute reduction in 60-day mortality (36% versus 21%; $p = 0.0047$) in dexamethasone-treated patients compared to usual care [83].

Methylprednisolone is equally as effective as dexamethasone in the treatment of Covid-19, and some studies have demonstrated better outcomes in Covid-19 hypoxic patients treated with methylprednisolone compared to dexamethasone [84]. Ranjbar et al. [84] compared the efficacy of 2 mg/kg per day of intravenous methylprednisolone with 6 mg/day of dexamethasone.

Methylprednisolone resulted in a shorter hospital stay and less need for mechanical ventilation. Moreover, methylprednisolone demonstrated better outcomes in Covid-19 hypoxic patients when compared with dexamethasone [84].

Additionally, several systematic reviews and meta-analyses indicate that corticosteroid therapy reduces all-cause death in patients with ARDS, and disease progression, rather than increasing adverse events [85,86]. Glucocorticoids reduce mortality rates in both ARDS patients, and SARS-CoV-2-associated ARDS, and the need for IMV. Covid-19 and non-Covid-19 ARDS patients respond favorably to all the formulation of corticosteroids (dexamethasone, hydrocortisone, prednisone, and methylprednisolone), inappropriate therapeutic dosages equivalent to dexamethasone 6 mg daily [86]. Nevertheless, the COVID-19 STEROID2 Randomized Trial demonstrated that among patients with COVID-19 and severe hypoxaemia, 12 mg/day of dexamethasone compared with 6 mg/day of dexamethasone did not result in statistically significant more days alive without life support at 28 days [87]. Therefore, very high doses of dexamethasone are not necessary, because they may aggravate immunosuppression, particularly when co-administered with IL-6R antagonists or JAK inhibitors.

Despite the multiple systemic adverse effects of corticosteroids, such as delayed viral clearance, and immunosuppression likely to result in opportunistic infections, cardiovascular, and metabolic side effects; the World Health Organization (WHO) strongly recommends corticosteroid therapy for patients with severe and critical Covid-19 disease [88].

Remdesivir

There are several therapeutic agents which have been evaluated for the treatment of Covid-19, however, no antiviral agents are specifically effective in the treatment of SARS-CoV-2 infection [89,90]. The most promising antiviral agent for the treatment of Covid-19 is remdesivir. Remdesivir (GS-5734) is an inhibitor of the viral RNA-dependent, RNA polymerase with in vitro inhibitory activity against SARS-CoV-1, and the Middle East respiratory syndrome (MERS-CoV) [91-95]. Remdesivir was developed by Gilead Sciences for the treatment of Ebola virus disease in 2016 [96], but is now universally used to treat severe Covid-19.

In a large double-blind, randomized, placebo-controlled trial, remdesivir is superior to placebo at reducing the duration of recovery in hospitalized patients with Covid-19 (one-category recovery, mean 7 versus 9 days) [95]. Patients in the remdesivir group had a shorter time to discharge than the placebo group (mean, 8 versus 12 days). Remdesivir significantly reduced adverse events related to respiratory failure due to Covid-19 [95]. Furthermore, the Kaplan-Meier estimates of mortality were lower in patients treated with remdesivir compared to placeblo on day 15 (6.7% versus 11.9%), and on day 29 (11.4% versus 15.2%) [95]. The therapeutic benefits in recovery persisted when adjustment was made for glucocorticoid use [95], which suggests that the efficacy of remdesivir may be additive to that of

dexamethasone therapy shown in the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial [75]

Nonetheless, other randomized, double-blind clinical trials have shown no statistically significant clinical improvement in hospitalized adults treated with remdesivir in patients with severe Covid-19 [97,98]. Piscoya et al. [98] in a systemic, meta-analysis of randomized clinical trials reported that the efficacy and safety of 10-day remdesivir were scarce.

Based on overwhelming positive results, remdesivir was issued an Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) on May 1, 2020, to permit the use of remdesivir for the treatment of adults, and children hospitalized for laboratory-confirmed Covid-19 [99]. Remdesivir has also received full or conditional approval in several countries for the treatment of severe Covid-19. Currently, remdesivir in combination with dexamethasone is the most used regimen for the treatment of severe SARS-CoV-2 in hospitalized patients, who require IMV or ECMO.

Remdesivir is administered via an intravenous injection with a loading dose on day one of 200 mg in adults, followed by daily maintenance of 100 mg daily for up to 10 days. The dosages are adjusted for body weight in pediatric patients (aged ≥12 years and weighing ≥40 kg) [99].

Lopinavir/Ritonavir

Lopinavir, and ritonavir are inhibitors of HIV protease. The combination of lopinavir-ritonavir (Kaletra) was approved by the FDA for the treatment of AIDS in 2000. In a randomized, open-label clinical trial in adult patients with severe Covid-19, Kaletra did not meet the endpoints. The dual combination did not reduce the risk of death, improve clinical outcomes, or decrease throat viral RNA in patients with severe Covid-19 [89]. In hospitals where it is used, it is administered orally as lopinavir/ritonavir 400/100 mg twice daily. Several other antiviral agents are in different phases of clinical trials for the treatment of Covid-19, such as favipiravir, ribavirin, darunavir, molnupiravir, and umifenovir [100].

On December 23, 2021, the FDA issued an emergency use authorization for Merck's molnupiravir for the treatment of mild-to-moderate Covid-19 in adults with laboratory positive SARS-CoV-2 viral testing [101]. Molnupiravir (Lagevrio) is an antiviral that introduces errors into the SARS-CoV-2 virus' genetic code, which prevents the virus from further replicating [102]. Lagevrio is administered as 400 mg or 800 mg capsules orally, twice daily for 5 days only. Table 3 lists the antivirals in clinical trials, or approve for emergency authorization use for the treatment of Covid-19.

The mortality rate due to Covid-19 is very high despite the use of antiviral agents, such as remdesivir, lopinavir, and ritonavir; and systemic corticosteroids. There is unmet need to develop novel therapeutic

agents, which can inhibit the inflammatory cascade of the cytokine storm due to Covid-19 infection, including targeting and inhibiting specific cytokines, such as IL-6 or its receptor (IL-6Rα).

Interleukin-6 plays a key role in the pathogenesis of SARS-CoV-2. Several biologics targeting the IL-6 receptor, and downstream signaling kinases, such as Janus Kinase 1 (JAK1), JAK2, and JAK3 have been developed for the treatment of autoimmune diseases, cytokine release syndromes, including Covid-19. Currently, there are several IL-6R antagonists, and JAK inhibitors in clinical trials for the treatment of COVID-19 disease, such as tocilizumab, and sarilumab (IL-6R mAb); baricitinib, ruxolitinib, and tofacinib (JAKs inhibitors). Table 4 shows the monoclonal antibodies in clinical trials for the treatment of Covid-19.

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody (mAb) that inhibits the binding of IL-6 to both membrane-bound receptors (mIL-6Rs), and soluble receptors (sIL-6Rs), and thus inhibiting downstream signaling, and biological effects of IL-6. Tocilizumab (Actemra) is an effective drug that is used to treat chronic rheumatic inflammatory diseases and vasculitis. It is approved for the treatment of rheumatoid arthritis in more than 100 countries [103,104], juvenile idiopathic arthritis (JIA) [105], giant cell arteritis (GCA) [106], cytokine release syndrome (CRS) during chimeric antigen T cell therapy (CAR-T [107], and for Takayasu arteritis in Japan (TAK) [108].

Several clinical trials and systemic meta-analyses have shown clinical benefits of tocilizumab treatment in patients with severe Covid-19 [109-113]. In a large meta-analysis study comprising 10201 patients with COVID-19, tolicizumab treatment resulted in a lower risk of mortality, and need for mechanical ventilation, especially in critically ill patients [111]. Patients treated with tocilizumab had a significantly better prognosis compared with patients treated with the SoC, in patients who required mechanical ventilation ($P = 0.02$). Pooled estimates of hazard ratio showed that tocilizumab treatment predicted significantly better overall survival in COVID-19 patients ($P = 0.01$), especially in critically ill patients ($P < 0.00001$) [111]. Furthermore, a French [114], and an Italian [115] retrospective study have confirmed the beneficial effects of add-on tocilizumab in patients with severe Covid-19 in reducing the need for invasive mechanical ventilation, and death.

The RECOVERY trial in the United Kingdom is one of the largest clinical trials to evaluate the efficacy and safety of tocilizumab in 4116 hospitalized patients with severe Covid-19, including 3385 (82%) patients who were receiving corticosteroids [113]. In patients with hypoxia, and systemic inflammation, tocilizumab improved the clinical outcomes, and survival regardless of the amount of respiratory support, and additional benefits from systemic corticosteroids [113]. Patients who received tocilizumab were more likely to be discharged from the hospital within 28 days compared to those who received usual care (57% versus 50%; rate ratio 1.22; 1.12-1.33; $P < 0.0001$). In a sub-group of patients not

receiving mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of mechanical ventilation or death (35% versus 42%; risk ratio 0.84; 95% CI 0.77-0.92; P < 0.0001). The mortality rate in 2022 patients allocated tocilizumab was 31%, and in 2094 patients who received the usual care was 35% within 28 days (rate ratio 0.85; 95CI 0.76-0.94; P = 0.0028) [113]. The results of the RECOVERY clinical trial mirrors those of the REMAP-CAP study in critically ill COVID-19 patients, which demonstrate a reduction in mortality in patients randomized to receive tocilizumab compared with usual care (28% versus 36%) [113].

The results from the RECOVERY trial demonstrate the efficacy and safety of tocilizumab in a broad clinical spectrum of the severity of Covid-19, from patients with moderate Covid-19 to severely hypoxaemic patients in respiratory failure requiring invasive mechanical ventilation. Although the majority of the patients in the study (82%) were receiving corticosteroids, tocilizumab monotherapy might be effective, particularly in a nonhospitalized patient with mild-to-moderate SARS-CoV-2. However, severely critically ill patients with SARS-CoV-2 on respiratory support require the synergistic beneficial effects of both corticosteroids and tocilizumab, or tocilizumab plus remdesivir or spike protein inhibitors, such as bamlanivimab, casirivimab, and etesevimab [116]. There is of course the risk of combining tocilizumab with another IL-6R antagonist or tocilizumab with a JAK inhibitor, including baricitinib, and Tofacitinib [117], because of the risk of opportunist infections, and helminths infestation. Janus kinases signal multiple immunobiological pathways used by most cytokines, including IL-6. Inhibiting IL-6 with biologic antagonists, and also blocking JAKs would result in severe immunosuppression, and other unrevealed pathologies. It is recommended that tocilizumab should not be co-administered with baricitinib.

Not all the clinical trials found beneficial effects of tocilizumab in a hospitalized patient with severe Covid-19 requiring HFNO and invasive mechanical ventilation. Some, multicentre observational, and placebo-controlled randomized clinical trials have demonstrated minimal or no clinical improvement with treatment with tocilizumab in hospitalized patients with severe SARS-CoV-2 [118-122]. Rosas et al. [122] have shown that in 294 patients randomized to receive tocilizumab, the biologic did not result in significantly better clinical status, or lower mortality compared to placebo at 28 days. The cumulative percentage of patients who received mechanical ventilation or who had died by day 28 was 12-0% in the tocilizumab group, and 19.3% in the placebo arm (P = 0.04). The mortality rate in the tocilizumab group was 10.4%, and 8.6% in the placebo group. Tocilizumab was safe, and well-tolerated by the patients, and there were no significant differences in adverse events between tocilizumab and placebo [122].

Salama et al. [123] have reported that in hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival. Death due to Covid-19 or any other cause occurred in 10.4% of the patients on tocilizumab, and 8.6% in patients who received the usual care by day 28 [123].

Similarly, Rosas et al. [124] in the REMDACTA trial in a patient with severe COVID-19, most of whom required NIV or IMV plus HFNO, did not observe the mortality benefit of tocilizumab. The 28-day mortality rate was 18% for patients randomized to receive tocilizumab, and 20% in the placebo group [124].

Overall, tocilizumab is a safe and effective biologic for the treatment of patients with various severity of Covid-19, particularly when administered early in the course of the illness. It has been shown to prevent the need for invasive mechanical ventilation, and death. It synergistically potentiates the anti-inflammatory effect of corticosteroids [113]. Tocilizumab may be very beneficial in outpatients with mild-to-moderate Covid-19.

Recent guidelines recommend that tocilizumab should be given in combination with a course of dexamethasone or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg daily. Tocilizumab was offered emergency use authorization by the FDA on June 25, 2021 [125]. The drug received EUA for hospitalized patients who are receiving systemic corticosteroids, and requiring supplemental oxygen, mechanical ventilation, or ECMO. It is administered as an intravenous infusion at the dosage of 8 mg/kg; not to exceed 800 mg/dose, up to 14 days or until hospital discharge [125].

Treatment with tocilizumab may be associated with an increased risk of helminth infestation, such as disseminated strongyloidiasis [126,127], especially in combination with corticosteroids [128]. Some clinicians recommend strongyloides prophylaxis in patients with Covid-19 on treatment with IL-6 antagonists, and corticosteroids [128].

Sarilumab

Sarilumab (Kevzara) is a fully human immunoglobulin G1 (IgG1) monoclonal antibody which binds to both membrane-bound IL-6Rα (mIL-6Rα), and soluble IL-6Rα (sIL-6Rα) with high affinity. It is approved by the FDA for the treatment of moderate-to-severe rheumatoid arthritis.

The affinity of sarilumab to the IL-6Rα chain is 20-times higher than that of tocilizumab [129,130]. Similarly, the dissociation constant of sarilumab for the target receptors is 12.8 pmol, which is about 55-times lower than that of tocilizumab, which is consistent with its higher binding affinity [131]. Given the impressive pharmacokinetics of sarilumab, one expects both sarilumab and tocilizumab to have similar biotherapeutic effects. However, this is not the case in some clinical trials with sarilumab in the treatment of severe Covid-19, requiring NIV and IMV, or HFNO.

The CORIMUNO-19 clinical trial was a multicentre, open-label, randomized study that evaluated the efficacy and safety of sarilumab in 148 patients with moderate-to-severe Covid-19 pneumonia (68 patients in the sarilumab group, and 80 in the usual care group) [132]. In this French study, sarilumab

treatment did improve the clinical outcome and mortality. Eighteen patients (26%) out of 68 patients in the sarilumab group had a WHO-Clinical Progression Scale (CPS) of greater than 5 at day 4 versus 20 (26%) of 79 in the usual care arm. On day 14, 25 (37%) of the patients receiving sarilumab, and 26 (34%) of the patients in the usual treatment group needed mechanical ventilation or died [132].

In a smaller open-label, randomized, controlled clinical, dose-ranging trial in 115 patients hospitalized for Covid-19 pneumonia, early use of sarilumab was reported to be associated with a low risk of ARDS, and requiring HNFO or mechanical ventilation [133]. Eleven (28%) of the patients in the control group, ten (27%) in the sarilumab 200 mg group, and 5 (13%) in the sarilumab 400 mg developed ARDS, requiring HFNO or respiratory support. The numbers of patients who died were: three in the control group, four in the sarilumab 200 mg, and none in the sarilumab 400 mg [133]. These results do not impressively portrait the efficacy of low dose sarilumab in preventing the need for mechanical ventilation, and in mortality benefit (4 deaths versus 3); except for the good safety profile.

Conclusion

SARS-CoV-2 is fatal severe pneumonia that may progress rapidly to respiratory failure and need for invasive mechanical ventilation and has a very poor prognosis. The standard of care of Covid-19, includes HFNO, dexamethasone, remdesivir, and NIV, IMV, or ECMO in very severe cases. However, mortality is exceptionally high even with these therapies. IL-6 plays a key role in orchestrating the cytokine storm, and hyperinflammation characteristic of Covid-19, leading to respiratory failure, and multi-organ failure. Two IL-6Rα antagonists have been issued a EUA by the FDA, including tocilizumab, and sarilumab. Interleukin-6 receptor antagonists are safe, and effective in the treatment of severe Covid-19, particularly in patients requiring HFNO, or respiratory support. Tocilizumab is the most studied IL-6Rα blocker in the treatment of severely ill patients with Covid-19. Tocilizumab co-administered with dexamethasone is superior to the standard of care alone in the treatment of hypoxemic patients requiring IMV. The duet has been shown to reduce the need for mechanical ventilation and to reduce the mortality in critically ill patients with Covid-19.

Conflict of interest:

The author declares that the publication was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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