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Review of Anti-inflammatory and Antiviral Therapeutics for Hospitalized Patients Infected with Severe Acute Respiratory Syndrome Coronavirus 2

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KEY POINTS

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to dysregulated cytokine production causing imbalance in host immunity.
- Glucocorticoids, such as dexamethasone, decrease mortality in hospitalized patients with SARS-CoV-2 requiring oxygen.
- Early use of interleukin-6 antagonists is beneficial for hypoxemic patients with COVID-19.
- Janus kinase inhibition is effective in preventing SARS-CoV-2 progression and has the potential to decrease mortality in patients requiring low-flow oxygen but not in those with severe symptoms.
- Antiviral therapy with remdesivir, intravenous immunoglobulin, or convalescent plasma is not beneficial in hospitalized symptomatic patients.

INTRODUCTION

Inflammation in Sepsis and Acute Respiratory Distress Syndrome

Sepsis is defined as a dysregulated host response to infection with an imbalance of proinflammatory and anti-inflammatory cytokines.[1] As the first line of defense to

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infection, the innate immune system is activated and produces proinflammatory cytokines leading to indiscriminate destruction of foreign or infected cells. Proinflammatory mediators then further trigger downstream physiologic processes leading to activation of coagulation pathways, endothelial dilatation and increased permeability, complement activation, recruitment of adaptive immunity, and ultimately, production of anti-inflammatory cytokines to balance the proinflammatory state.[2] When left unchecked, hyperinflammation may occur, resulting in tissue damage, acute respiratory distress syndrome (ARDS), vasodilatory shock, disseminated intravascular coagulopathy, intravascular formation of microthrombi, and death. This unchecked hyperinflammatory state is sometimes referred to as "cytokine storm."[3]

During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in 2020, some hospitalized patients with severe SARS-CoV-2 infection were reported to have lymphopenia and thrombocytopenia, as well as elevated acute phase reactants, such as ferritin and C-reactive protein (CRP), and raised liver enzymes and D-dimer.[4] Not surprisingly, the derangement of these biomarkers was directly associated with worse outcomes.[5] The inflammatory profile of patients with moderate to severe SARS-CoV-2 infection is similar to that of patients with ARDS and sepsis.[5–7] In a prospective study, Wilson and colleagues[6] compared the cytokine profiles of patients with coronavirus disease 2019 (COVID-19) with historical patients suffering from ARDS or sepsis. They found no difference in 6 major cytokines (interleukins [IL]-1β, IL-1RA, IL-6, IL-8, IL-18, and tumor necrosis factor [TNF]-α).

Immune Response in Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Elevated cytokine concentrations are associated with increased severity of SARS-CoV-2 infections.[8] The pathogenesis of SARS-CoV-2 infection includes various phases (Fig. 1). In the early phase, the virus enters the cells after binding of the spike unit to the angiotensin-converting enzyme 2 receptor.[9] The host cell protease facilitates viral fusion and cell entry following which viral RNA processing occurs. The viral N-protein inhibits interferon production, which decreases recruitment of innate immunity cells and viral clearance.[9–11] As viral replication continues, host cell death ensues, resulting in the release of excessive intracellular material, including cytokines and chemokines. Symptomatically, the host experiences hypoxemia and can develop ARDS and additional organs dysfunction. A myriad of cytokines may be involved in this process.[12] Clinical trials have demonstrated improved outcomes in patients with severe or critical COVID-19 with immunomodulatory therapies. In this article, the authors review the current level of evidence.

IMMUNE MODULATION IN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTIONS
Glucocorticoids

Glucocorticoids are fat-soluble hormones that bind to transmembrane receptors as well as intracellular receptors. In the setting of stress, glucocorticoids are released by the adrenal glands and bind to the glucocorticoid receptor, a transcription factor in target cells. Glucocorticoid receptor binding has strong anti-inflammatory downstream effects ranging from transcriptional action, protein modification, and direct cell type–specific directives (Table 1).[13] A variety of glucocorticoids, including dexamethasone, prednisone, hydrocortisone, and methylprednisolone, have been trialed; the largest study, conducted by the RECOVERY collaborative group, examined dexamethasone.[14–17] Therapy with dexamethasone has become standard of care for patients with SARS-CoV-2 requiring oxygen therapy.
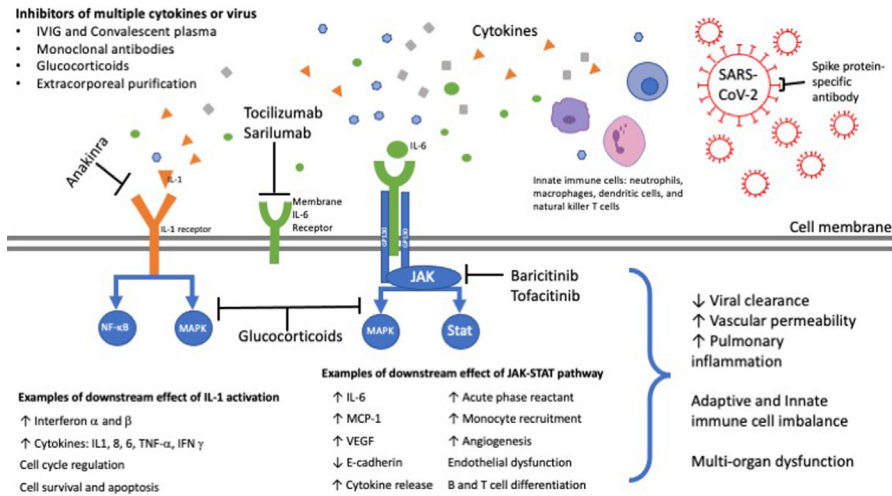
Fig. 1. Potential targets for anti-inflammation and antiviral in SARS-CoV-2 infection.[12,33,59] (*Adapted from* Ni, Y., Alu, A., Lei, H. et al. Immunological perspectives on the pathogenesis, diagnosis, prevention and treatment of COVID-19. Mol Biomed 2, 1 (2021). https://doi.org/10.1186/s43556-020-00015-y; under CC BY 4.0 http://creativecommons.org/licenses/by/4.0/.)

Timing of steroids

Uncontrolled inflammation can result in progression from severe to critical SARS-CoV-2 infection. Careful selection of the right cohort of patients to receive glucocorticoids for pan-immune suppression is key, as premature immune modulation may impede viral clearance. Historically, the use of steroids in critically ill patients infected with influenza, SARS-CoV-1, or Middle East respiratory syndrome coronavirus has not demonstrated any benefit in patient-centered outcomes, but is associated with delayed viral clearance.[18–20] Indeed, the early use of systemic steroids in patients with SARS-CoV-2 with mild symptoms is likely to be harmful. Sahu and colleagues[21] conducted a systematic review of the use of systemic steroids using data of 2214 patients included in 3 randomized controlled trials (RCTs) and 4 propensity score matched studies. They demonstrated that in patients without oxygen requirement, steroid therapy was associated with an increased risk of disease progression. The mean duration to viral clearance was also longer in the group receiving glucocorticoids compared with the control arm (18.9 days vs 16.5 days; odds ratio [OR] 0.20, 95% confidence interval [CI] 0.04–0.36).[21]

However, SARS-CoV-2 inflammation in moderate to severe disease behaves differently. The RECOVERY trial,[14] the largest steroid trial in SARS-CoV-2 to date, was an open-label, RCT and included 6525 patients of whom 2104 patients were assigned to receive dexamethasone and 4321 were assigned to receive usual care. At the time of randomization, 24% of patients were not on oxygen; the remainder were either on noninvasive oxygen therapy (61%) or on invasive mechanical ventilation (16%). The study demonstrated a reduction in 28-day mortality (OR, 0.83; 95% CI, 0.75–0.93) in patients receiving steroids. However, in those who did not require oxygen therapy at time of randomization, there was no significant benefit (OR, 1.19; 95% CI, 0.92, 1.55), and a trend toward harm. A meta-analysis of 7 RCTs by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapeutics (REACT) Working Group consistently demonstrated that patients with respiratory symptoms

Table 1
Glucocorticoid mechanisms of action in severe acute respiratory syndrome coronavirus 2

Effects of Glucocorticoids	Action
Genomic actions	• Direct and indirect binding through other transcription factors • Decrease of IL-2 expression through AP1, NFAT, and NFKB • Shift from TH1 cellular immunity to TH2 humoral immunity through decrease of IL-2, IFN-γ, and STAT4 • Chromatin structure alteration by interaction of histone acetyltransferase activity
Nongenomic actions	• Direct negative interaction with PI3K, JNK, 14-3-3 proteins in T-cell receptor signaling complex • Enters thymocyte mitochondria and induces apoptosis • Recruitment of multiprotein chaperone complex for signaling pathways
Cell type–specific actions	• Monocyte and macrophage survival and function: improves phagocytic activity and stimulates clearance of harmful elements • Dendritic cells: Maturation, survival, and migration toward lymph nodes. Reduces ability of DC cells to stimulate T cells by upregulation of costimulatory IL-6, IL-12, and TNF-alpha, and tolerance-inducing transcription factors • Neutrophils: Leukocyte extravasation and favoring their egress from bone marrow and modulating their migration to perivascular space • T cells: Decreases number by migration back to bone marrow or lymphoid tissues with induction of chemokines. Favors T-cell apoptosis. Limits naïve T-cell differentiation
Hemodynamic effects	• Potentiation of vasoconstrictor hormones • Retention of fluid

Abbreviations: AP1, activator protein 1; DC, dendritic cell; NFAT, nuclear factor of activated T cells; NFKB, nuclear factor-κB; PI3K, Phosphoinositide 3-kinase; TH, T helper.

Adapted from Liberman AC, Budziñski ML, Sokn C, Gobbini RP, Steininger A and Arzt E (2018) Regulatory and Mechanistic Actions of Glucocorticoids on T and Inflammatory Cells. Front. Endocrinol. 9:235. https://doi.org/10.3389/fendo.2018.00235; under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

requiring oxygen benefited from systemic glucocorticoid therapy with the largest benefit seen in those on mechanical ventilation.[17] The beneficial role of steroids on systemic inflammation is further supported by a decrease in mortality in patients with a prolonged course of illness (>7 days of symptoms).[17]

Currently, the evidence for the use of systemic glucocorticoids for persistent diffuse lung parenchymal disease is limited. In an observational cohort study, 4.8% of survivors of severe SARS-CoV-2 infections had residual symptoms and persistent radiographic evidence of interstitial lung disease with a predominant organizing pneumonia pattern 4 weeks after initial hospital admission.[22] It is recommended to involve multidisciplinary medical teams to determine the best course of action in this patient population.[22,23]

Glucocorticoid selection

Hydrocortisone is the equivalent of cortisol when used as a drug; other formulations are compared with hydrocortisone,[13] in terms of potency and duration of action. Dexamethasone is the most potent anti-inflammatory and longest-acting corticosteroid followed by methylprednisolone, prednisone, and hydrocortisone (least potent). They have all been used to treat oxygen-requiring patients with SARS-CoV-2 infection.

Dexamethasone is known to suppress IL-1 signaling pathways, specifically c-Jun N-terminal kinase (JNK)-p38, leading to suppression of macrophage release of downstream cytokines, such as IL-6, IL-8, and TNF.[24] Similarly, hydrocortisone use in patients with severe sepsis has been shown to significantly decrease IL-1β, interferon-γ (IFN-γ), TNF-α, and IL-6 levels.[25] Methylprednisolone has been reported to have some benefit in acute lung injury.[26]

Dexamethasone, hydrocortisone, and methylprednisolone have been used in ARDS clinical trials. In the DEXA-ARDS study, Villar and colleagues[27] investigated the role of dexamethasone (20 mg for 5 days followed by 10 mg for 5 more days). Hospital mortality was reduced by 12.5% (95% CI, −22.9 to −1.7) with an increase in ventilator-free days of 4.8 (95% CI, 2.57–7.03) in those treated with dexamethasone.

The COVID-19 Dexamethasone RCT has been completed in Brazil.[28] It included mechanically ventilated patients with moderate to severe ARDS who were randomized to receive 20 mg of dexamethasone for 5 days followed by 10 mg of dexamethasone for 5 additional days. There was not a significant difference in all-cause mortality between the 2 groups, in contrast to the original DEXA-ARDS results.[27,28] Furthermore, both the CAPE-COVID (community-acquired pneumonia-COVID) trial and the randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) trial randomized patients to 200 mg of daily hydrocortisone (equivalent of dexamethasone 7 mg) or placebo.[15] There was no significant mortality benefit or difference in organ support-free days.[15,29] Methylprednisone infusion also did not lead to significant mortality benefits.[16] None of the studies showed differences in serious adverse events between the glucocorticoid and placebo arms.

The RECOVERY trial compared Dexamethasone 6 mg daily for 10 days versus standard care and demonstrated a significantly lower mortality.[14] Although there was no significant difference between dexamethasone 6 mg per day versus 12 mg per day in clinical outcomes, the mortality at 28 and 90 days trended toward benefit in the higher dose group in the COVID STEROID 2 Trial.[30] Smaller clinical trials examining the use of other formulations and different dosages of hydrocortisone and methylprednisolone were examined in a meta-analysis by the WHO-REACT working group.[17] Significant benefit was seen in the dexamethasone subgroup and not in either hydrocortisone or methylprednisolone subgroups groups.

In conclusion, current evidence supports the use of dexamethasone 6 mg daily for 10 days in hospitalized patients with SARS-CoV-2 requiring oxygen therapy (Table 2). Steroids should be avoided in asymptomatic or mild disease. Increasing the dose to 12 mg can be considered. The actions of dexamethasone are likely to be more systemic rather than intrapulmonary.

Interleukin-6 Antagonists

IL-6 is a key cytokine in the pathogenesis of severe to critical SARS-CoV-2 infection. Cellular stress induces IL-6 secretion.[12] IL-6 receptors are soluble and transmembrane structures.[31] After binding with IL-6, the IL-6 receptor complex binds with another molecule gp130 in either membrane form or soluble form in blood. The membrane-bound gp130-IL-6/IL-6 receptor complex is associated with Janus kinase (JAK), a tyrosine kinase.[32] The binding of soluble gp130 to the IL-6 receptor complex has an inhibitory effect on IL-6 downstream activities (see Fig. 1). IL-6–mediated clinical signs include patients' fever, weight loss, flulike symptoms, and an elevation in acute phase reactants like CRP.[32] In addition, angiogenesis is triggered, and neutrophils are recruited to the site of inflammation. IL-6 also promotes B- and T-cell differentiation and is involved in the differentiation of naïve T cell to CD4+ T-helper cells. Inflammation with elevated IL-6 levels can be seen in severe to critical SARS-CoV-2

Table 2			
Anti-inflammatory therapeutics with evidence-based data in support of use			
Therapeutics	**Dose**	**Timing**	**Benefit**
Glucocorticoids: Dexamethasone	6 mg daily for 10 days, oral or intravenous	Hospitalized patients requiring oxygen	Decreased mortality
IL-6 antagonists: Tocilizumab	400 mg or 8 mg/kg (maximum 800 mg) single dose Use with systemic glucocorticoids	Hospitalized patients requiring oxygen or noninvasive ventilatory support Not in patients treated with mechanical ventilation or ECMO More effective in patients with CRP ≥75 mg/L	Decreased mortality
JAK inhibitors: Baricitinib	4 mg daily for up to 14 days, orally. Use with systemic glucocorticoids	Hospitalized patients requiring oxygen	Faster time to symptom resolution Potential decrease mortality

Abbreviation: ECMO, extracorporeal membrane oxygenation.

infection,[25,33] and excessive IL-6 levels may lead to an imbalance in innate and adaptive immunity.[34] Therefore, IL-6 antagonism has a role in the management of severe critical COVID-19.

Multiple studies have examined the efficacy of using a fixed-single dose of tocilizumab 400 mg or weight-based dose at 8 mg/kg, or sarilumab at 400 mg intravenously in hospitalized patients with SARS-CoV-2 with variable results.[35–42] A potential explanation for the different findings may be administration of the drug at different stages of the disease process and severity of illness. The largest study was the RECOVERY trial, which compared tocilizumab with placebo in 4116 patients; most participants concurrently received dexamethasone.[38] Study drug was initiated at a median of 2 days from hospital admission. A substantial proportion of patients did not require ventilatory support (45%); 41% received noninvasive ventilation (NIV), and a small group required mechanical ventilation. There was a 15% reduction in 28-day mortality (OR, 0.58; 95% CI, 0.76–0.74). A subgroup analysis revealed that there was no benefit in those on ventilatory support, or in those not receiving concomitant corticosteroids. The REMAP-CAP group enrolled 865 patients, with mostly patients on high-flow nasal cannula (29%) or NIV (42%); 29% of patients were already on invasive mechanical ventilation.[37] Patients were randomized within 24 hours of initiation of respiratory support. The study was stopped early after an interim analysis showed significantly more days alive without need for organ support in patients treated with tocilizumab (OR, 1.64; 95% CI, 1.24–2.14) or sarilumab (OR, 1.76; 95% CI, 1.17–2.91) compared with placebo. Patients in the intervention arm were more likely to survive to hospital discharge (pooled OR, 1.64; 95% CI, 1.15–2.35).[37] Subgroup analysis showed that in patients on mechanical ventilation, treatment with an IL-6 antagonist did not improve outcomes

(adjusted OR, 1.27; 95% CI, 0.84–1.94). Other smaller clinical studies showed mixed results, most likely because of the inclusion of patients with variable severity of disease,[36,39–41,43] and lack of concomitant steroid use. Three of these trials included moderate patients on low-flow nasal canula,[36,39,40] whereas others included patients who were already on mechanical ventilation in critical disease.[41,43,44] The heterogeneity of disease severity within the studies might have impacted the outcome of the analysis.

A meta-analysis by the WHO REACT group including 27 studies comparing IL-6 antagonists with usual care or placebo showed an overall all-cause mortality reduction of 14% (OR, 0.86; 95% CI, 0.79–0.95).[35] In a subgroup analysis, the benefit of IL-6 antagonism was only seen with concomitant use of corticosteroid use. In addition, the protection from IL-6 antagonism was more pronounced in patients with CRP $\geq$ 75. Indeed, a follow-up report of the CORIMUNO-TOCU-1 study showed that a CRP cutoff of 150 mg/L was associated with reduced 90-day mortality (OR, 0.18; 95% CI, 0.04–0.89).[45] Furthermore, patients with critical disease requiring mechanical ventilation or extracorporeal membrane oxygenation were least likely to benefit in contrast to patients treated with supplemental oxygen or NIV.[35]

In conclusion, early use of IL-6 antagonists is beneficial for hypoxemic patients with COVID-19 requiring oxygen (see **Table 2**). The use of IL-6 receptor inhibitor therapy in patients on mechanical ventilation is likely too late and unlikely to improve outcomes. IL-6 antagonists should be used in conjunction with corticosteroids. CRP levels may identify individuals with more potential to benefit.

Janus Kinase Inhibitors

The JAK-signal transducer and activator of transcription (JAK-STAT) signaling pathway mediates extracellular interleukins and interferons signal, through membrane receptor activation, and leads to T-cell proliferation and maturation.[46] Cytokine receptor binding phosphorylates JAK and allows docking for cytoplasmic STATs (see **Fig. 1**).[12] JAK phosphorylates STAT protein, allowing STAT to move into the nucleus. STAT regulates inflammatory and immune response, viral clearance, cell proliferation and survival, endothelial integrity, and coagulation pathways.[47] IL-6 receptor downstream activity is mediated by JAK-STAT pathway; specifically, IL-6 receptor activation of STAT3 is associated with lung fibrosis and injury, thrombosis, and delayed viral clearing by blocking IFN response of STAT-1. The rationale for baricitinib was based not only on its anti-inflammatory property to inhibit JAK but also on the ability to inhibit other kinases associated with viral endocytosis.[48] In addition, the JAK-STAT pathway mediates angiotensin II function in the cardiovascular system.[31] An observational study in patients with SARS-CoV-2 showed that baricitinib significantly reduced CRP and increased T-lymphocyte count with an increase of the CD4$^+$ to CD8$^+$ cell ratio.[49] Reduction in STAT3 activity improves NK cell-mediated surveillance against pathogens and blocks the release of inflammatory cytokines.

RCTs investigating JAK antagonists are limited. Two international studies used oral baricitinib at 4 mg per day for 14 days with dose adjustment for impaired renal function.[50,51] The first study using a JAK-inhibitor was the Adaptive COVID-19 Treatment Trial 2 study, which included 1033 patients of whom 68.3% had moderate disease (National Institute of Allergy and Infectious Disease Ordinal Scale [NIAID-OS] 4 [no oxygen] and 5 [low-flow supplemental oxygen] and 31.6% had severe symptoms [NIAID-OS 6 using NIV or high flow oxygen]).[51] Patients were randomized to a combination of remdesivir with baricitinib or remdesivir alone. In this study, patients receiving glucocorticoid treatment were excluded. Patients treated with the combination of

remdesivir and baricitinib were more likely to recover to no or mild symptoms (NIAID-OS 1–3) 1 day faster (rate ratio [RR], 0.16; 95% CI, 0.10–1.32). There was no survival benefit with combination therapy of remdesivir and baricitinib. The exclusion of glucocorticoid treatment is an important limitation of this study.

The COV-BARRIER study, another trial examining the role of baricitinib, included participants treated with dexamethasone at a dose of 20 mg/d or less. Most patients (63.4%) had moderate disease (NIAID-OS 5), and 24.4% had NIAID-OS 6.[50] There was no difference in progression on the ordinal scale or death between the baricitinib and placebo arm. However, all-cause 28-day mortality was lower in the baricitinib group (hazard ratio, 0.57; 95% CI, 0.41–0.78). This protective effect persisted to 60 days. A subgroup analysis investigating the impact of different oxygen requirements at the time of randomization showed that patients who required NIV or high-flow oxygen had significantly lower 28-day mortality, regardless of concomitant steroid use.

The STOP-COVID group tested the efficacy of another JAK 1, 2, and 3 inhibitor, tofacitinib, in 289 hospitalized patients with mild to moderate disease.[52] Patients were randomized to receive oral tofacitinib 10 mg twice a day for 14 days versus placebo. At day 28, the composite outcome of death or respiratory failure (NIAID-OS 6 or more) was lower in the tofacitinib versus placebo arm (18.1% vs 29.0%; RR, 0.63; 95% CI, 0.41–0.97). A meta-analysis of observational studies and clinical trials using the JAK inhibitors, baricitinib or ruxolitinib, showed lower mortality in the treatment group (RR, 0.42; 95% CI, 0.30–0.56).[53]

In summary, JAK inhibition is effective in preventing SARS-CoV-2 progression and has the potential to decrease mortality in patients requiring low-flow oxygen but not in those with severe symptoms. JAK inhibitors should be used concomitantly with glucocorticoids (see **Table 2**).

Anakinra

IL-1β is transcribed by monocytes, macrophages, and dendritic cells following Toll-like receptor activation by pathogens.[54] IL-1 binding triggers protein complexes at the intracellular membrane with 2 further downstream pathways: activation pathway for cellular survival and inhibitory pathway for B-cell maturation.[55,56]

The use of anakinra in mild to moderate SARS-CoV-2 infection was not supported by a recent RCT.[57] One hundred sixteen patients were randomized to receive anakinra versus usual care. Only a small proportion of the patients received glucocorticoids (14%). There was no difference in terms of symptom progression at day 4 and day 14 in the primary outcomes and the overall survival.

ANTIVIRAL THERAPY FOR HOSPITALIZED SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 *INFECTION*
Antiviral Drugs

In the early phase of the COVID-19 pandemic, multiple antiviral drugs were repurposed as potential to treat SARS-CoV-2 infection, including lopinavir-ritonavir and remdesivir.[58,59] The viral protease inhibitor combination, lopinavir-ritonavir, is not effective in SARS-CoV-2 infection.[58,60,61] Remdesivir is an inhibitor of viral RNA-dependent RNA polymerase. In a large RCT including 1062 patients, remdesivir decreased time to recovery by 5 days, and this overall effect was mostly driven by patients receiving oxygen.[59] In patients with severe to critical infection at time of enrollment, remdesivir did not shorten time to recovery. Ultimately, the meta-analysis by the WHO Solidarity group did not show a mortality benefit with the use of remdesivir regardless of subgroups by age or by severity of infection.[60] Furthermore, the WHO

living guideline suggests against the use of remdesivir in hospitalized patients with SARS-CoV-2 infection.[62]

New antiviral drugs against SARS-CoV-2 are rapidly emerging as this review is being prepared. Molnupiravir, an oral prodrug of ribonucleoside analogue against RNA viruses, has good tolerability and potential in decrease viral load in early SARS-CoV-2 infection.[63,64] Further phase 3 studies are necessary to determine the efficacy.

Hyperimmune Immunoglobulin and Convalescent Plasma

In viral infection, intravenous immunoglobulin (IVIG) has been proposed to provide passive immunity to mediate antibody-dependent cellular cytotoxicity and acts as decoy receptor to prevent viral binding and entry.[65] However, no large RCT for efficacy has been published to date. In a meta-analysis of 7 observational studies, use of IVIG in critically patients with SARS-CoV-2 (n = 122) was associated with decreased mortality (RR, 0.57; 95% CI, 0.42–0.79).[66] However, no mortality reduction was seen in severe patients (n = 201; RR, 0.76; 95% CI, 0.51–1.14) or moderately ill (n = 92; RR, 1.39; 95% CI, 0.23–8.29) patients.[66] Trends in hospital or intensive care unit length of stay were inconsistent among the studies, as was the dosing of IVIG.[66]

Similar to the concept of using immunoglobulin binding, convalescent plasma from a previously SARS-CoV-2–infected individual was initially thought to potentially confer passive immunity in currently infected individuals. In a multicenter, double-blinded RCT of 334 patients with moderate SARS-CoV-2 symptoms, convalescent plasma infusion failed to improve clinical status at 30 days.[67] The RECOVERY study group tested the efficacy of convalescent plasma in 11,558 patients with most of them requiring oxygen in the hospital (87%).[68] There was no mortality or other clinical benefit in the treatment group. A large meta-analysis found no efficacy associated with the use of convalescent plasma and pointed out the high risk of bias in the included studies.[69]

Neutralizing Monoclonal Antibody

Two combinations of neutralizing antibodies: casirivimab with imdevimab (Regen-COV) and bamlanivimab with etesevimab, targeting SARS-CoV-2 surface spike protein decrease viral load compared with placebo in patients with mild to moderate symptoms.[70,71] Used in the ambulatory settings, these monoclonal antibody cocktails prevent hospitalization.[71,72] However, hospitalized patients treated with anti–SARS-CoV-2 antibodies did not have different symptom progression compared with standard of care.[73] The RECOVERY study examined the use of casirivimab with imdevimab in hospitalized patients only and found mortality benefit in a subgroup of patients who were seronegative of SARS-CoV-2 at time of randomization.[74]

Plasma Exchange and Absorption

Limited data are available for the use of plasma exchange in patients with severe to critical SARS-CoV-2 infection. An open-label study randomized patients to therapeutic plasma exchange and usual care. There was no significant mortality benefit despite sustained decrease in IL-6 levels.[75] Currently, there is no clinical evidence to support the use of these methods.[76–78]

SUMMARY

SARS-CoV-2 infection leads to dysregulation of immune pathways. Therapies focusing on suppressing cytokine activity demonstrate some success. Current evidence supports the use of dexamethasone in hospitalized patients requiring oxygen.

Early use of IL-6 inhibitors is also beneficial in hypoxemic patients. CRP level can serve to identify patients who may benefit from IL-6 inhibitors. JAK inhibition in combination with glucocorticoids is emerging as a potential therapeutic option for patients with moderate to severe symptoms. Direct antiviral therapy is not effective in hospitalized patients with severe symptoms. Data on anakinra, hyperimmune immunoglobulin/ convalescent plasma, or plasma purification are limited and inconclusive.

CLINICS CARE POINTS

- Severe and critical syndrome from Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mainly driven by dysregulation of host inflammatory response.
- Anti-inflammatory therapy using dexamethasone 6 mg daily for 10 days for SARS-CoV-2 infected patients requiring supplemental oxygen decreases mortality in this population.
- Biologics such as interleukin-6 antagonists in early severe syndrome and Janus kinase inhibition in low flow oxygen-requiring patients are also effective in improving the outcomes of this population.

DISCLOSURE

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