Immunomodulatory Agents for Coronavirus Disease-2019 Pneumonia

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Immunomodulatory treatment • Corticosteroids • JAK inhibitors

KEY POINTS

- Hyperinflammatory response to severe acute respiratory syndrome coronavirus 2 contributes to severe inflammation, acute lung injury, and end-organ damage.
- Many immunomodulatory agents have been tested to attenuate inflammatory responses associated with coronavirus disease-2019 (COVID-19).
- Corticosteroids, specifically dexamethasone, have been shown to reduce mortality in hospitalized patients with COVID-19 who require supplemental oxygen.
- Interleukin-6 antagonists and Janus kinase inhibitors have shown mortality benefits in patients with COVID-19 requiring supplemental oxygen.

INTRODUCTION

The primary cause of morbidity and mortality in coronavirus disease-2019 (COVID-19) pneumonia is acute hypoxemic respiratory failure, an inability to maintain adequate gas exchange caused by severe inflammation and tissue damage in the lungs of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1–3] The inflammatory response observed in the lungs infected with SARS-CoV-2 is multifactorial and of variable severity, ranging from mild cases that remain largely asymptomatic to cases of severe respiratory failure requiring mechanical ventilation and in some cases, extracorporeal membrane oxygenation (ECMO).[1,4,5] Early on the course of the pandemic, it became clear that these variable clinical presentations reflected individual differences in immune response and inflammation resolution, underscoring the possibility of using immunomodulatory therapies to avoid or mitigate respiratory failure in COVID-19 pneumonia.

The immune response to SARS-CoV-2 infection in the lungs is complex and includes a proinflammatory state characterized by increased innate immune cell activation and an abnormal inflammatory cytokine response that exacerbates local inflammation and immune cell recruitment to the lungs.[4,6–12] In early studies to define circulating and local markers of severe COVID-19 presentations and clinical outcomes, cytokines such as interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor α (TNFα), and other nonspecific markers of inflammation such as C-reactive protein (CRP) and ferritin were frequently dysregulated at different stages, providing an initial focus for the selection and timing of immunomodulatory therapies.[4,6,8,13–15]

Upon entering epithelial cells and interacting with immune cells in the respiratory tract, the double-stranded SARS-CoV-2 RNA activates cytoplasmic pathogen recognition receptors (eg, MDA5, toll-like receptors [TLRs]) to activate an

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early but dysfunctional type I and type III interferon (IFN) response.[16–22] Type I and III IFN responses during SARS-CoV-2 induce the expression of numerous antiviral IFN-stimulated genes (ISGs) that promote cytokine secretion, recruitment, and activation of innate immune cells such as mononuclear phagocytes (monocytes and macrophages) and neutrophils, and also the recruitment and activation of adaptive immune cells such as B and T cells that play a critical role in SARS-CoV-2 immunity.[23–26] There is evidence that while early type I and III IFN to SARS-CoV2 may be impaired, delayed IFN responses and their interaction with IL-1β signaling may lead to excessive inflammation through stimulation of IL-6 and TNFα secretion.[14,26–28]

The continued innate immune cell recruitment and activation and a hyperinflammatory response to the virus lead to widespread alveolar epithelial and vascular endothelial damage, associated with capillary extravasation, inflammatory infiltrate, cell death, and microvascular thrombosis.[7,8,29–31] Both alveolar epithelial cell types, AT1 and AT2 are affected in this process, leading not only to impairments in gas exchange through AT2 lesion but the impaired secretion of pulmonary surfactants and host defense proteins through AT1 cell injury.[8,32] In addition to epithelial injury, endothelial damage also contributes to cytokine (IL-6, IL-8, and CCL2) and prothrombotic factor release (eg, PAI1 or SERPINE1), exacerbating inflammatory recruitment, capillary leakage, and microvascular thrombosis.[31,33–35]

In addition to the essential role of epithelial cells in the inflammatory response to SARS-CoV-2, immune cells play a crucial role in COVID-19 pathogenesis.[8,10,32,36] Monocytes and monocyte-derived airway macrophages play a critical role in the development of COVID-19 pathogenesis.[30] Dysfunctional monocyte and macrophage populations were detected in the lungs of those with severe presentations, characterized by impaired antigen presentation, proinflammatory transcriptome profiles, and impaired expression of pro-resolving genes (eg, increased expression of CCL2 CCL3, CXCL1, CXCL3, CXCL8, CXCL10, IL-1β, and TNFα).[8,10,11,22,37,38] In addition to recruited cells, alveolar macrophages expressed high levels of CCL7, CCL8, and CCL13, which may further exacerbate adaptive and innate immune cell recruitment to affected areas.[11] Although neutrophils are not the predominant cell type encountered in the airways of patients with COVID-19, they play an essential role as effectors of these pro-inflammatory changes and likely drivers of tissue injury in COVID-19.[8,39,40] The excessive release of neutrophil extracellular traps (NETs) and tissue proteases by neutrophils and abnormal cell survival programs expressed by these cells exacerbate the alveolar and epithelial injury and promote further lung inflammation through cell death and poor clearance of inflammatory debris.[37,41,42]

On the basis of these findings, a large number of studies were published in the past three years targeting specific cell populations or inflammatory cytokines, aiming to minimize the proinflammatory features of COVID-19 to minimize its clinical impact or enhance the protective effects of early IFN response.[15,43–45] For example, depletion of mononuclear phagocyte populations in animal models infected with SARS-CoV2 improved survival from infection, mediated through decreased CCL2, TNFα, and IL-6 signaling.[22] Consistently, CCR2-deficient mice, with impaired ability to recruit monocytes had increased cytokines responses and viremia, suggesting that monocytes and their products are essential to COVID-19 pathogenesis.[46] Concurrently, immune modulation studies in human subjects diverged into a broad immunosuppressive approach using corticosteroids or targeted approaches aimed at minimizing the effects of excessive cytokine responses as was the case with targeted IL-6 and IFN signaling modulation.[15,43,45,47]

Corticosteroids

Corticosteroids are broad immunosuppressing agents that can reduce systemic inflammatory responses and therefore decrease the severity of illness in several infectious syndromes.[44,48,49] Corticosteroids were commonly used for this reason during the 2002 to 2004 severe acute respiratory syndrome (SARS) and were shown to improve oxygenation, decrease fever, and overall hospital length of stay and mortality.[49] Therefore, corticosteroids were thought to be potentially beneficial during the COVID-19 pandemic.[44,48,49] **Table 1** summarizes the key studies that sought to evaluate the role of corticosteroids in the treatment of COVID-19.

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial demonstrated that the use of corticosteroids decreased mortality in patients who are hospitalized for COVID-19.[44] This decreased mortality, however, has only been demonstrated in patients with severe COVID, that is, those who are hospitalized and require supplemental oxygen. Benefit has not been demonstrated in non-severe COVID-19, that is, nonhospitalized patients or those who are hospitalized but are not requiring oxygen.[50,51] Furthermore, studies have revealed hospitalized patients

Table 1
Systemic corticosteroids

Clinical Trial Name	Study Type	Study Population	Interventions	Outcomes	Limitations	Conclusion
RECOVERY[44]	Open-label RCT	Hospitalized patients with COVID-19	2:1 random assignment of usual standard of care (SOC) alone (n = 4321) or standard of care plus oral of IV dexamethasone (n = 2104) 6 mg daily for up to 10 days (or hospital discharge whichever was sooner)	All-cause mortality at 28 days: All patients: 23% in dexamethasone arm versus 26% in SOC arm (RR 0.83; 95% CI, 0.75–0.93; P < 0.001) Receipt of mechanical ventilation (MV) or ECMO at randomization: 29% in dexamethasone vs 41% in SOC (RR 0.64, 95% CI 0.51–0.81) Receipt of supplemental oxygen but not MV at randomization: 23% dexamethasone versus 26% in SOC (RR 0.82; 95% CI,0.72–0.94) Patients not requiring supplemental oxygen at randomization: 18% dex versus 14% SOC (RR 1.19, 95% CI, 0.92–1.55)	Open-label Did not evaluate cause-specific mortality, adverse events and subgroups to look at comorbidities Patients on supplemental oxygen had varying degrees of severity	Dexamethasone reduced 28-day mortality in hospitalized patients who required supplemental oxygen with the greatest benefit being demonstrated in patient requiring MV.

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Clinical Trial Name	Study Type	Study Population	Interventions	Outcomes	Limitations	Conclusion
CoDEX[52]	Open-label RCT	Hospitalized COVID-19 patients with MV within 48 h of meeting criteria for moderate-to-severe ARDs (PaO2/FiO2 $\leq$ 200 mm HG)	Random 1:1 assignment of dexamethasone 20 mg IV daily for 5 days then 10 mg daily for 5 days or until ICU discharge (n = 151) or SOC (n = 148)	Mean number of days alive and free from MV by Day 28: 7 in dexamethasone arm vs 4 in SOC arm (P = 0.04) No differences between arms in all-cause mortality (56% vs 62%), number of ICU-free days, duration of MV, or score on 6-point OS Mean SOFA score at Day 7: 6.1 in DEX arm vs 7.5 in SOC arm (P = 0.004) Post hoc analysis of probability of death or MV by Day 15: 68% in dexamethasone arm vs 80% in SOC arm (OR 0.46)	Open-label Underpowered Patient discharged before 28 days were not followed for re-hospitalization or death Approximately 25% of patients who were randomized to SOC alone received corticosteroids	Dexamethasone increased the number of days alive and MV free in 28 days in moderate-to-severe ARDS patients with COVID-19.

REMAP-CAP[53]	Randomized Open-label adaptive trial	Hospitalized COVID-19 patients with severe COVID-19 requiring ICU admission for respiratory or cardiovascular support	1:1:1 randomization of hydrocortisone 50 mg IV every 6 h for 7 days (n = 137), shock-dependent hydrocortisone 50 mg IV every 6 h for up to 28 days (n = 146), or no hydrocortisone (n = 101)	No difference between in median number of organ support-free days at Day 21 (0 in each arm) No difference between arms in in-hospital mortality (30% in fixed-dose hydrocortisone arm vs 26% in shock-dependent hydrocortisone arm vs 33% in no hydrocortisone arm)	Open-label Terminated early therefore underpowered	Hydrocortisone did not increase median number of support-free days
Crothers et al.[51]	Observational cohort study	27,168 patients admitted to a VA hospital for COVID-19 within 14 days after testing positive	Corticosteroids (95% of patients received dexamethasone) administered within 48 h of admission (n = 7507) Compared with no corticosteroids administered (n = 7433)	Risk of all-cause mortality at 90 days was higher in those who received dexamethasone: For combination of those not on supplemental oxygen and those on low-flow nasal cannula oxygen: HR 1.59; 95% CI, 1.39–1.81 For those not on supplemental oxygen: HR 1.76; 95% CI, 1.47–2.12 For those on low-flow nasal cannula oxygen: HR 1.08; 95% CI, 0.86–1.36	Retrospective observational study Variation in other therapies patients received	Dexamethasone in hospitalized COVID-19 patients who were receiving low-flow nasal cannula during the first 48 h of admission did not show a mortality benefit. There was an increase in mortality seen in patients who received dexamethasone who were not on supplemental oxygen within the first 48 h after admission.

not requiring supplemental oxygen may have worse outcomes when corticosteroids are used, as suggested by a large observational cohort study done in veterans administration (VA) patients.[51] Corticosteroids are not without their side effects, which include hyperglycemia, secondary infection, and psychiatric effects. Therefore, use in mild COVID-19 is not recommended at this time due to the lack of adequate positive data and potential for side effects.[44,50,51]

The COVID-19 Dexamethasone study (CoDEX) and *Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia* (REMAP-CAP) are the two largest studies done to date looking specifically at the role of corticosteroids for COVID-19 in the hospital setting.[52,53] CoDEX, which was a randomized open-label trial, demonstrated that dexamethasone increased the number of days alive and mechanical ventilation-free days in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) COVID-19 patients. However, this study was terminated early and therefore was underpowered. In addition, many of the patients in the standard-of-care arm also received corticosteroids, which makes interpreting the results of the trial challenge.[52] REMAP-CAP compared outcomes using a fixed dose, shock-dependent dosing of hydrocortisone versus the standard of care with no hydrocortisone. There was no difference in the number of days alive and mechanical ventilation-free days in patients with severe COVID-19 requiring respiratory or cardiovascular support.[53]

The differences in the clinical outcomes in these studies suggest that the timing of corticosteroids in the treatment of COVID-19 is important. Using corticosteroids early in treatment may result in worsening outcomes given the effect of corticosteroids on the immune system's ability to fight off the virus earlier on in the infection. As the disease progresses and the cytokine storm begins corticosteroids become beneficial in preventing additional damage and subsequently poor outcomes. However, once there is progression to a severe disease requiring respiratory or cardiovascular support, the benefit may be diminished due to the extensive damage that likely has already been done.[48,49,52,53]

The systemic corticosteroid that has been most studied is dexamethasone. However, the current National Institute of Health (NIH) guidelines recommend that if dexamethasone cannot be used that other equivalent dose of a systemic corticosteroid is substituted. A few studies have evaluated the effects of different doses of dexamethasone but given the mixed results of those studies 6 mg daily is the recommended dose at this time. Therefore, equivalent doses for dexamethasone 6 mg would be prednisone 40 mg, methylprednisolone 32 mg, or hydrocortisone 160 mg. As dexamethasone has a longer half-life, it is given daily whereas prednisone and methylprednisolone are recommended to be given once or twice daily and hydrocortisone is recommended to be given two to four times daily.[53,54] The guidelines only recommend this therapy for hospitalized patients who require supplemental oxygen. It is important to note that this therapy is recommended for 10 days or until hospital discharge; it is not recommended to discharge patients on this therapy. The guidelines recommend against the use of dexamethasone or other systemic corticosteroids specifically for the non-hospitalized patient given the lack of data for this population. If patients are on a corticosteroid for another indication the guidelines recommend continuing it.[54]

In addition to systemic corticosteroids, inhaled corticosteroids, given their direct anti-inflammatory effects on the lungs, have also been studied for the treatment of COVID-19.[55–58] **Table 2** summarizes the four main randomized controlled trials that sought to evaluate the effects of this therapy on the treatment of COVID-19. PRINCIPLE and SOTIC used budesonide comparison to standard of care and CONTAIN and a study by Clemency and colleagues used ciclesonide compared with placebo.[55–58] CONTAIN used ciclesonide both as an inhalation as well as an intranasal preparation.[58] All of these studies evaluated non-hospitalized patients with COVID-19. PRINCIPLE evaluated high-risk patients, whereas the other studies were conducted in any patients who were not hospitalized. PRINCIPLE found a reduction in the time to patient's self-reported recovery, whereas the study by Clemency and colleagues and CONTAIN did not. PRINCIPLE did not find a reduction in COVID-19-reported hospitalization or death, whereas STOIC and the study by Clemency and colleagues found a decrease in need for urgent care/emergency department assessment and hospitalization. However, these trials had small sample sizes making conclusions from them difficult to interpret.[55–58] Given the mixed outcomes, the use of inhaled corticosteroids for the treatment of COVID-19 is not recommended at this time.[50]

Interleukin-6 Inhibitors

Early data from patients with COVID-19 suggested a correlation of elevated IL-6 levels with a hyperinflammatory response and severe ARDS. The elevated IL-6 was also linked to increased mortality.[13,48,59] This led to the idea that the use of IL-6

Table 2
Inhaled corticosteroids

Clinical Trial Name	Study Type	Study Population	Interventions	Outcomes	Limitations	Conclusion
PRINCIPLE[55]	Open-label RCT	Nonhospitalized COVID-19 patients with $\leq$ 14 days of symptoms and age $\geq$ 65 or $\geq$ 50 with comorbidities	1:1 random assignment of usual standard of care (SOC) alone (n = 787) or standard of care plus budesonide 800 mcg inhaled twice daily for 14 days (n = 1069)	Patients who were hospitalized or died due to COVID-19 within 28 days: 6.8% in budesonide arm vs 8.8% in usual care arm (OR 0.75; 95% CrI, 0.55–1.03) Median time to reported recovery: 11.8 days in budesonide arm vs 14.7 days in usual care arm (HR 1.21; 95% CrI, 1.08–1.36)	Open-label Relied on patient's self-report for time to recovery	Inhaled budesonide reduced time to patient's self-reported recovery, but not COVID-19-reported hospitalization or death.
STOIC[56]	Open-label phase 2 RCT	Nonhospitalized COVID-19 patients with $\leq$ 7 days of symptoms and age $\geq$ 18	1:1 random assignment of usual standard of care (SOC) alone (n = 73) or standard of care plus budesonide 800 mcg inhaled twice daily until symptom resolution (n = 73)	Median duration of budesonide use: 7 days Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm versus 14% in usual care arm (relative risk reduction 91%).	Open-label Small sample size	Inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization in adult outpatients with mild COVID-19.

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Clinical Trial Name	Study Type	Study Population	Interventions	Outcomes	Limitations	Conclusion
Clemency et al.[57]	Double-blind randomized controlled trial	Nonhospitalized COVID-19 patients with a positive test in the last 72 h age $\geq$ 12 with $\geq$ 1 symptom of fever, cough, or dyspnea	1:1 random assignment of placebo meter dose inhaler (MDI) (n = 203) or ciclesonide MDI 160 μg/actuation, 2 actuations twice a day for 30 days (n = 197)	Median time to alleviation of all COVID-19-related symptoms: 19 days in ciclesonide arm vs 19 days in placebo arm (HR 1.08; 95% CI, 0.84–1.38) By Day 30: Alleviation of COVID-19-related symptoms: 70.6% in ciclesonide arm vs 63.5% in placebo arm Subsequent ED visit or hospital admission for COVID-19: 1% in ciclesonide arm vs 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85) Hospital admission or death: 1.5% in ciclesonide arm vs 3.4% in placebo arm (OR 0.45; 95% CI, 0.11–1.84) No deaths seen at 30 days in either group	Relied on patient's self-report for alleviation of all symptoms Small sample size particularly for ED/hospitalization outcome	Inhaled ciclesonide did not reduce time to reported recovery; however, there was decrease in ED visits and hospitalization in the small sample size of events.

Contain[58]	Double-blind randomized controlled trial	Nonhospitalized COVID-19 patients age $\geq$ 18 with $\geq$ 1 symptom of fever, cough, or dyspnea and symptoms for $\leq$ 6 days	1:1 random assignment of saline placebo MDI and intranasal saline twice daily for 14 days (n = 98) or ciclesonide MDI 600 μg/actuation and intranasal ciclesonide 100 μg twice a day for 14 days (n = 105)	Percentage of patients with resolution of fever and all respiratory symptoms at Day 7: 40% in ciclesonide arm vs 35% in the placebo arm (adjusted risk difference 5.5%; 95% CI, −7.8% to 18.8%) Percentage of patients with resolution of fever and all respiratory symptoms at Day 14: 66% in ciclesonide arm vs 58% in placebo arm (adjusted risk difference 7.5%; 95% CI, −5.9% to 20.8%) Percentage of patients who were admitted to the hospital by Day 14: 6% in ciclesonide arm vs 3% in placebo arm (adjusted risk difference 2.3%; 95% CI, −3.0% to 7.6%)	Small sample size	Inhaled plus intranasal ciclesonide did not improve resolution of fever and respiratory symptoms in young healthy nonhospitalized patients with COVID-19

inhibitors could help mitigate the inflammatory response and reduce pathological damage from COVID-19 infection.[60]

This idea was not novel, as IL-6 inhibitors have been previously studied in the treatment of cytokine release syndrome. Tocilizumab, siltuximab, and sarulimab have been found to be effective in cytokine storm diseases such as hemophagocytic lymphohistiocytosis (HLH), idiopathic multicentric Castleman's disease and chimeric antigen receptor (CAR) T-cell-induced cytokine storm.[60–66]

The potential benefits of IL-6 inhibitors have been well studied, specifically with tocilizumab. Several randomized controlled trials demonstrated a benefit for tocilizumab in the treatment of COVID-19 (**Table 3**). The RECOVERY trial was a large open-label randomized controlled trial that studied the addition of tocilizumab in patients with hypoxemia and CRP $\geq$ 75. Tocilizumab resulted in a reduction in 28-day mortality/mechanical ventilation and increased hospital discharge; notably, 16% of participants in the tocilizumab arm did not actually receive the drug.[67] REMAP-CAP showed a reduction in mortality and an increase in organ-free support days when tocilizumab was administered within 24 h of ICU admission after starting organ support, which included the need for noninvasive or invasive mechanical ventilation, vasopressors, or inotropes. Sarilumab had a similar outcome in this trial, but the sample size for these patient groups was very low.[68] EMPACTA found a reduction in the need for mechanical ventilation but no difference in mortality in hospitalized patients not requiring mechanical ventilation; the treatment arm ended up including a portion of patients who did not require any oxygen at all.[69]

Randomized controlled clinical trials of tocilizumab that demonstrated unfavorable outcomes have potential flaws in study design involving timing of administration. REMDACTA was a well-designed study that showed no benefit of tocilizumab when administered to patients requiring > 6L of oxygen. This could potentially be too late in the hyperinflammatory phase as some patients may have lower oxygen requirements but increasing inflammatory markers necessitating earlier administration of the drug.[70]

CONVACTA was another well-designed study showing no benefit of tocilizumab, but receipt of corticosteroids was allowed which likely confounded the effect of tocilizumab. There were also a significant number of patients who were mechanically ventilated or on ECMO, which represents a disease stage too late to benefit from tocilizumab as end-organ damage may have already occurred.[71] The BACC Bay study showed no difference for the prevention of intubation or death but included a portion of patients with COVID-19 who were not requiring any oxygen and had a small sample size.[72] The CORIMUNO-19 study targeted patients requiring at least 3L of oxygen and showed a numerical benefit of tocilizumab but was not statistically significant likely due to the lack of an adequate sample size.[73] In addition, the primary endpoint was set at 14 days, which is likely not long enough to appreciate significant differences given the protracted course of the disease. Lescure and colleagues was the only randomized controlled trial evaluating the use of sarilumab alone and showed no benefit in time to clinical improvement compared with placebo but was limited in their sample size.[74,75]

Collectively, these randomized controlled trials demonstrate the importance of tocilizumab as a treatment of COVID-19 for a high-risk patient at the optimal time during the course of disease before significant end-organ damage. This includes patients with escalating oxygen requirements and elevated inflammatory markers, such as CRP while receiving remdesivir and dexamethasone. Patients who are not showing these signs of a hyperinflammatory syndrome may not benefit from this drug. In addition, timing of administration is important as patients who have reached mechanical ventilation or ECMO may already have irreversible end organ damage from viral infection that may not be reversed by additional immunomodulating therapies. As of this writing, the other IL-6 inhibitors have not been well studied enough to recommend use.

Janus Kinase Inhibitors

As immune modulators, Janus kinase (JAK) inhibitors are potent molecules that inhibit the JAK/STAT pathway which results in reduced production of IL-1 and IL-6. Baricitinib reversibly inhibits JAK1/JAK2 which prevents the production of inflammatory cytokines.[76] In addition, baricitinib exerts an antiviral effect by inhibiting the clathrin-associated viral entry by suppressing 2 host kinases, AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK) which are responsible for clathrin-mediated endocytosis and viral endocytosis, respectively.[77] The immunomodulatory effects of baricitinib in SARS-CoV-2 infection were first noted in an *in-vitro* study of blood samples of patients with COVID-19 infection in which following the administration of 1000 nM of baricitinib, levels of interferon-gamma, IL-1β, IL-6, TNF-α, and other inflammatory cytokines were reduced.[78] Another study using the rhesus macaque model of COVID-19 infection reported

Table 3
Overview of randomized controlled trials for interleukin 6 inhibitors with the benefit

	Study Type	Study Population	Interventions	Outcomes	Limitations	Conclusion
RECOVERY[56]	Open-label RCT	Hospitalized COVID-19 patients with hypoxia and a CRP $\geq$ 75 mg/L	1:1 random assignment of tocilizumab 400–800 mg (n = 621) or placebo (n = 729) in addition to standard care	28-day mortality: 31% vs 35% (RR 0.85, 95%CI, 0.76–0.94; P = 0.003) Hospital discharge within 28 days: 57% vs 50% (RR 1.22, 95% CI, 1.12–1.33;P < 0.0001) Receipt of mechanical ventilation or death: 35% vs 42% (RR0.84, 95% CI0.77–0.92;P < 0.0001)	Open-label 16% of patients in tocilizumab actually did not receive treatment Random CRP cutoff	Tocilizumab reduced the probability of progression to mechanical ventilation and/or death and increased the probability of hospital discharge within 28 days.
REMAP-CAP[57]	Open-label adaptive platform RCT	Hospitalized patients with COVID-19 admitted in the ICU within 24 h after starting organ support	Random assignment of tocilizumab 8 mg/kg (n = 353), sarilumab 400 mg (n = 48), or standard care (n = 402)	*Tocilizumab vs control* Median organ support free-days (IQR): 10 (−1 to 16) vs 0 (−1 to 15) In-hospital survival: 28% vs 36% (aOR 1.64; 95% credible interval 1.14–2.35) *Sarilumab vs control* Median organ support free-days (IQR): 11 (0 to 16) vs 0 (−1 to 15) In-hospital survival: 22% vs 36% (aOR 2.01; 95% credible interval 1.18–4.71)	Open-label Control arm closed early	Tocilizumab and sarilumab increased the amount of organ-free support days and reduced in-hospital mortality.

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Table 3
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	Study Type	Study Population	Interventions	Outcomes	Limitations	Conclusion
EMPACTA[58]	Double-blind placebo-controlled RCT	Hospitalized patients with COVID-19 not receiving mechanical ventilation	2:1 random assignment of tocilizumab 8 mg/kg (n = 249) or placebo (n = 128) in addition to standard care	Mechanical ventilation or death at day 28: 12% vs 19.3% (HR 0.56, 95% CI 0.33–0.97; P = 0.04) Death at day 28: 10.4% vs 8.6% (weighted difference 2 95% CI, −5.2 to 7.8)	Sample size somewhat small especially in placebo group 9% of patients did not require oxygen at baseline, this population may not benefit from this therapy	Tocilizumab reduced the need for mechanical ventilation but did not have an effect on mortality.

baricitinib reducing inflammation and lung pathology.[79] Several studies using JAK inhibitors have shown positive results (Table 4).

The first randomized, placebo-controlled clinical trial which assessed baricitinib for the treatment of COVID-19 was the Adaptive Covid-19 Treatment Trial 2 (ACTT-2). In this trial, patients were randomized to receive remdesivir plus baricitinib versus remdesivir plus placebo. The primary clinical endpoint was time to recovery and the main secondary outcome was clinical status at day 15 using an ordinal scale. In both groups, the majority of patients were receiving supplemental oxygen (86%) with 20.9% and 10.7% of patients receiving oxygen through high-flow devices/noninvasive ventilation and invasive mechanical ventilation/ECMO, respectively.[80] The patients who received combination therapy with remdesivir and baricitinib recovered a median 1 day faster than the control group who received remdesivir and placebo (median 7 days versus 8 days, respectively), with a hazard ratio 1.15. The effect of baricitinib was most pronounced for the group receiving high-flow oxygen/noninvasive ventilation where the median time to recovery was 10 days in the combination group and 18 days in the control group with a rate ratio [RR] for recovery of 1.51. For the key secondary outcome of odds of clinical improvement at day 15, the overall odds ratio (OR) of improvement was greater in the combination group than the control group (OR 1.3). As with the primary outcome, the OR of clinical improvement was greatest in the group receiving high-flow oxygen/noninvasive ventilation at 2.2. Finally, 28-day mortality was 5.1% in the combination therapy group compared with 7.6% in the control group with a hazard ratio (HR) for death to be 0.65. The greatest difference in mortality between the two groups was noted in the group receiving supplemental oxygen, 1.9% versus 4.7% (HR 0.40) and in the group receiving high flow oxygen/noninvasive ventilation 7.5% versus 12.9% (HR 0.55).[80]

A major limitation of the ACTT-2 trial was the low usage of concomitant glucocorticoids as part of the treatment regimen for COVID-19. The study was conducted before the results of the RECOVERY trial which revealed a mortality benefit for patients in COVID-19 in the dexamethasone treatment group. Of the whole cohort in the ACTT-2 trial, only 223 patients (21.5%) received glucocorticoids. An analysis of this group of patients revealed a ratio for recovery of 1.06 and a lack of an effect on the overall results for the ACTT-2 trial. However, even with this caveat, the ACTT-2 trial demonstrated that immune modulation with baricitinib benefited patients requiring oxygenation, especially those who required high-flow/noninvasive ventilation. The lack of benefit in patients receiving mechanical ventilation or ECMO suggested that the end organ damage due to COVID-19 inflammatory effects was not responsive to the immunomodulatory effects of baricitinib.[80]

The COV-BARRIER study evaluated baricitinib in hospitalized patients, who were randomized to receive baricitinib, 4 mg daily, versus matched placebo for up to 14 days. The composite primary endpoint was the proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death by day 28.[45] 88% of the patient enrolled required supplemental oxygen. Of the 1518 patients in the trial, 1204 received systemic corticosteroids, a key therapy that reduced mortality in this patient population. Only a minority of patients (18.9%) received remdesivir.[45] Of the baricitinib group, 27.8% compared with 30.5% receiving placebo progressed to meet the composite the primary endpoint (OR 0.85, $P = 0.180$). However, there was a significant mortality benefit for hospitalized patients with COVID-19. The endpoint of 28-day all-cause mortality was 8% in the baricitinib group compared with 13% in the placebo group (HR 0.57, $P = 0.0018$). This was a 38.2% relative reduction in mortality with an estimated 1 additional death prevented per every 20 patients treated with baricitinib.[45]

The RECOVERY trial was the largest study to evaluate baricitinib in hospitalized patients with COVID-19. Patients were randomly allocated to usual care plus baricitinib 4 mg daily for 10 days or until discharge (if sooner) versus usual care. A total of 8156 patients were randomly allocated to receive baricitinib plus usual care in addition to usual care alone. In this patient population, 95% of the patients received corticosteroids and 32% received tocilizumab either at the time of randomization or within 24 h of randomization. Overall, 514 (12%) of 4148 patients in the baricitinib group versus 546 (14%) of 4008 patients allocated to usual care died within 28 days (age-adjusted rate ratio 0·87; $P = 0·028$), for a reduction in mortality of 13%. was smaller than seen in smaller studies.[81]

Other JAK inhibitors which have been studied in the treatment of COVID-19 include ruxolitinib and tofacitinib. Although the initial ruxolitinib studies had favorable outcomes data, the sample sizes were small and the study designs were either retrospective, or non-randomized prospective studies.[82–85] However, in the largest international randomized, double-blind placebo-controlled studies with ruxolitinib, favorable results were not seen. RUXCOVID was a phase III study that evaluated the efficacy and safety of ruxolitinib versus

Table 4
Overview of negative clinical studies of immunotherapeutic targets and respective trials

Drug	Target/ Mechanism of Action	Trial Name	Study Type	Study Population	Inflammatory Requirements for Enrollment	Respiratory Requirements for Enrollment	Primary Endpoint	n in Intervention Arm; n in Placebo Arm	Conclusion
Adalimumab[90]	TNF inhibitor	N/A	Double-Blind RCT	Hospitalized patients with severe COVID-19 Pneumonia receiving remdesivir and dexametha-sone	N/A	SpO2 <93% on room air or mechanical ventilation or ARDS	Mechanical ventilation, ICU admission, and rate of mortality	34; 34	No benefit to using adalimumab in combina-tion with remdesivir and dexametha-sone
Canakinumab[86]	IL-1β antagonist	CAN-COVID	Double-Blind RCT	Hospitalized patients with Severe COVID-19 Pneumonia	CRP >20 mg/L or ferritin >600 mg/L	Hypoxemic but not mechanically ventilated	Survival without the need for invasive mechanical ventilations from Days 3 through 29	227; 227	No statistical difference between intervention and placebo arms in proportion of patients who survived without mechanical ventilation
Mavrilimumab[91]	GM-CSF Inhibitor	MASH-COVID	Double-Blind RCT	Hospitalized Patients with Severe COVID-19 pneumonia and systemic hyperinflamma-tion	CRP >5 mg/dL	SpO2 <92% on room air or required supplemental oxygen, patients on MV excluded	Alive and off supple-mental oxygen at day 14	21; 19	No evidence of improved supplemental oxygen-free survival by Day 14

Otilimab[92]	GM-CSF inhibitor	OSCAR	Double-Blind RCT	Hospitalized patients with Severe COVID-19 pneumonia	CRP or ferritin > ULN	HFNC Oxygen, NIV, or MV < 48 h before dosing	Alive and free of respiratory failure at Day 28	395; 398	No evidence of reduced probability of respiratory failure of death
Ruxolitinib[89]	JAK-1 and JAK-2 inhibitor	RUXCOVID	Double-Blind RCT	Hospitalized patients with confirmed COVID-19 who were not mechanically ventilated or in the ICU	N/A	Respiratory rate greater than 30 breaths per minute, requiring supplementary oxygen, oxygen saturation of 94% or less on room air, P/F ratio of less than 300 mm Hg	Composite of death, respiratory failure (requiring invasive mechanical ventilation), or ICU care, by day 29	284; 144	No statistical difference in composite endpoint nor in secondary individual outcomes
Vilobelimab[93]	C5a inhibitor	PANAMO	Double-Blind RCT	Hospitalized patients with severe PCR- and radio-graphically confirmed COVID-19	N/A	Mechanically ventilated patients	28-day all-cause mortality	185; 184	No statistical difference in mortality[a]

[a] Prespecified subanalysis of patients showed a statistically significant reduction in mortality.

placebo in hospitalized patients with severe COVID-19 requiring oxygen support. However, patients who were intubated or in the ICU at the time of randomization were excluded from the evaluation of the primary outcome. A total of 432 patients were randomized in a 2:1 fashion to receive ruxolitinib 5 mg every 12 h versus placebo. An equal number of patients received corticosteroids and remdesivir in each arm. There were no differences in the composite primary endpoint of death and respiratory failure requiring mechanical ventilation between the two groups. Secondary outcomes of mortality and ICU care by day 29, and duration of hospitalization were also similar in both groups. The RUXCOVID trial did not demonstrate the efficacy of ruxolitinib compared with a placebo in the treatment of severe COVID-19.[86]

Tofacinitib was evaluated in the STOP-COVID trial where 289 patients with severe COVID-19 were randomized to receive tofacitinib 10 mg versus placebo every 12 h up to 14 days (or until day of discharge, which was sooner). Patients who were receiving noninvasive or invasive mechanical ventilation as well as ECMO were excluded. Baseline characteristics were similar in both groups where 63.2% of the tofacitinib group received supplemental oxygen and 13.2% received high-flow oxygen compared with 62.1% and 12.4% in the placebo group, respectively. Approximately 80% of patients in each arm received corticosteroids. The antiviral oseltamivir was administered in 13.9% of the tofacitinib group compared with 12.4% in the placebo group.[87] The primary outcome of death or respiratory failure through day 28 occurred in 18.1% of the patients who received tofacitinib compared with 29.0% who received placebo (risk ratio 0.63; 95% CI, 0.41 to 0.97, $P = 0.04$).[87]

Which immune modulator is best for the treatment of severe COVID-19 remains an unresolved question. Aside from corticosteroids, tociluzimab and baricitinib have been the most extensively studied. Baricitinib is an oral agent and can also be administered via an enteral feeding tube in critically ill patients. However, it cannot be administered to patients with severely impaired renal function (ie, eGFR < 15 mL/min).[88] Tocilizumab is usually administered intravenously in hospitalized patients which may be useful in patients who are cannot take anything enterally. On the contrary, tocilizumab can be administered safely in patients with an (eGFR<15 mL/min).[89] However, there is no prospective, randomized controlled trial comparing the two agents in the treatment of COVID-19. A retrospective, multicenter cohort compared baricitinib to tocilizumab, of the 382 patients, 194 (50.8%) received tocilizumab, and 188 (49.2%) received baricitinib and found no significant difference in the outcomes of hospital discharge within 60 days alive and freedom from mechanical ventilation.[90]

Baricitinib reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen in addition to standard care which included corticosteroid therapy. The cumulative efficacy data led the US Food and Drug Administration to grant approval to baricitanib for the treatment of severe COVID.[91] Further research is needed to assess whether baricitinib and tocilizumab are equivalent therapies for severe COVID-19 in hospitalized patients.

Additional immunomodulatory agents that have not demonstrated benefit

Although some therapeutics targeting immunomodulation have been found to be efficacious in clinical trials, many more, even within the same drug class, have not. Much emphasis has been placed on the IL-6 and IL-1 axis as the data for these targets have been the most promising to date. However, the trial results have not all been congruent with clinical improvement. Canakinumab, an IL-1β antagonist, has shown no improvement in survival without mechanical ventilation in a randomized control trial of 454 patients with COVID-19 pneumonia.[92] On the contrary, anakinra, another IL-1 antagonist, was shown to have some potential clinical benefit.[93,94] However, differences in the designs of these trials may have directly affected the results. In the canakinumab trial, CRP and ferritin were used as indicators of acute inflammation, whereas in the anakinra trial soluble urokinase plasminogen activator receptor (suPAR) was used. Chronic inflammatory conditions such as obesity and smoking are known to lead to increased suPAR levels whereas CRP is generally unaffected by these levels. By using suPAR in lieu of CRP, the anakinra trial may have selected for a group of patients who were demonstrating acute on chronic inflammation as opposed to the acute inflammation required for enrollment in the canakinumab trial. This may indicate that canakinumab, and other IL-1β antagonists may prove to have increased benefit when used earlier in the disease process.

In a similar scenario, ruxolitinib, a JAK inhibitor, did not show any improvement in death, worsening respiratory failure, or ICU admission at 28 days.[89] This is compared with other kinase inhibitors such as baricitinib and tofacitinib which have demonstrated at least partial benefit in patients hospitalized with severe COVID-19 pneumonia.[68] One of the key differences between these trials,

however, were the respiratory requirements to enroll patients. In REMAP-CAP, patients were eligible for enrollment if they were receiving either invasive or noninvasive ventilation, whereas in RUXCOVID the patients were required to not be mechanically ventilated. This may indicate that additional studies into ruxolitinib, and other JAK inhibitors, would be best designed for patients with higher degrees of respiratory support.

Other potential immunomodulatory therapeutic targets that have not yet panned out clinically include TNF-inhibitors such as adalimumab; granulocyte-macrophage colony-stimulating factor inhibitors such as mavrilimumab and otilimab; and C5a inhibitors such as vilobelimab.[95–98] Some of these trials have failed to reach statistical significance due to being underpowered, whereas others have found benefit only in subgroups. For example, vilobelimab was able to reach statistical significance in 28-day all-cause mortality in a prespecified sub-analysis of patients from Western European countries but not when all the patients were included.[93] There remain several promising therapies that target the hyperactivation of the immune system against COVID-19, but whether they will join the growing list of beneficial agents remains to be determined.

SUMMARY

Early in the COVID-19 pandemic, it became evident that the immune response to SARS-CoV-2 infection could lead to a hyperinflammatory state resulting in severe end-organ damage such as ARDS. To attenuate the immune response, studies of immunomodulatory agents were rapidly initiated to determine which potential agents and in which patient populations such agents would be of benefit. Consequently, we now know that patients with severe COVID-19 who require supplemental oxygen but do not require mechanical ventilation or ECMO may derive the greatest benefit from immunomodulatory therapy. Of the agents studied to date, the corticosteroid, dexamethasone, has the most robust state supporting its in reducing mortality in the patient who require supplemental oxygenation. Other agents, such as tocilizumab and the JAK inhibitors, baricitinib, and tofacitinib, have been also shown to reduce mortality in patients requiring high levels of supplemental oxygen despite the use of corticosteroids and/or remdesivir. Although much has been learned during the pandemic regarding attenuating the pathologic hyperinflammatory state associated with COVID-19, more research is still needed to determine if the IL-6 antagonism of tocilizumab or the JAK inhibitors are equivalent in their salutary effects in treating severe COVID-19 or if combining such agents would lead to a greater improvement in mortality.

CLINICS CARE POINTS

- Dexamethasone use should be limited to those who are hospitalized are require supplemental oxygen.
- Duration of treatment with dexamethasone for COVID-19 should be a maximum of 10 days or until hospital discharge whichever is first.
- If a patient requires additional immunomodulatory therapy in addition to dexamethasone interleukin-6 antagonist, tocilizimab, or Janus kinase inhibitor, baracitinib, should be considered as adjunctive therapy.

DISCLOSURE

The authors declare they have no conflict of interests.

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