The role of immunomodulatory medications in the treatment of COVID-19

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Purpose of review
Given the role of inflammation in severe forms of COVID-19, glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) have been assessed as potential COVID-19 therapies.

Recent findings
Randomized controlled trials (RCTs) have shown that glucocorticoids reduce mortality in severe COVID-19. RCTs of DMARDs have shown mixed results varying on intervention and inclusion criteria. DMARDs, including colchicine or biologic agents, may improve COVID-19 outcomes in specific patient populations.

Summary
Glucocorticoids are an effective treatment for the management of severe COVID-19. Further studies are needed to better define the patient populations who could benefit from DMARD use, as well as provide guidance regarding the timing of these interventions.

Keywords
COVID-19, disease-modifying antirheumatic drugs, glucocorticoids, hyperinflammatory

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory coronavirus (SARS-CoV-2), has led to an unprecedented global health crisis with over 170 million confirmed cases and over 3.7 million deaths as of June 2021 [1]. The severe forms of COVID-19, a hyperinflammatory syndrome characterized by lymphopenia and elevated transaminases, lactate dehydrogenase (LDH), ferritin, D-dimers, as well as elevated inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor-necrosis factor (TNF)-α and IL-8 have been described [2,3▪,4]. Some of these features have been identified as poor prognostic factors in patients with COVID-19, independent of other well-established risk factors such as older age, male sex, obesity, and increased comorbidity burden.

Given the resemblance to other hyperinflammatory conditions such as macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (HLH), or chimeric antigen receptor (CAR) T-cell induced cytokine release syndrome (CRS), several immunosuppressive therapies have been and are currently being investigated for the treatment of severe COVID-19. The aim of this review is to summarize data, primarily from randomized clinical trials, regarding the use of immunosuppressive treatments, including glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) for the treatment of COVID-19 up to May 30th, 2021.

RATIONALES FOR USE OF IMMUNOMODULATORS IN COVID-19

Infection of cells expressing angiotensin-converting enzyme 2 receptors by SARS-CoV-2 represents the initial phase of the disease [5]. The later stage, which is characterized by increased production of proinflammatory cytokines and chemokines such as IL-1, IL-6, TNF-α, and IL-8, mediates organ damage and failure leading to death in severe COVID-19 [6▪,7]. It is important to note that this two-phase approach is simplistic and that these processes occur concomitantly, resulting in infection of endothelial cells,

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KEY POINTS

- In patients with COVID-19 infection and oxygen requirements, glucocorticoids are associated with improved outcomes including mortality.
- Most recent randomized trials using IL-6 inhibitors have shown improvement in outcomes in patients with severe COVID-19 infection.
- Further studies are needed to clarify the role of other DMARDs for the treatment of COVID-19, including the specific patient populations that would benefit from such interventions.

both micro- and macrovascular thrombosis, tissue hypoxia, and cellular death [8].

Although DMARDs are predicted to minimize the hyperinflammation, Janus kinase (JAK) inhibitors could additionally have a role in the inhibition of viral entry by blocking AP2-associated protein kinase 1 (AAK1), a regulator of the endocytosis [9].

CLINICAL PHENOTYPE AND INCLUSION CRITERIA

The initial therapeutic approach to COVID-19 hyperinflammatory state was based on previous experiences with other hyperinflammatory syndromes such as MAS/HLH. However, recent studies comparing characteristics between these two conditions have highlighted some differences. Compared to MAS/HLH, which is characterized by activation of an IL-18-interferon-γ axis, COVID-19 hyperinflammatory state is characterized by elevation of IL-1 receptor antagonist, intracellular adhesion molecule 1, and IL-8, as well as reduced levels of soluble Fas ligand [10]. Also, a study evaluating patients with COVID-19 hyperinflammation showed that they did not fulfill MAS/HLH classification criteria such as the HScore and 2004-HLH diagnostic criteria, despite having evident hyperinflammation features [11].

Two different sets of criteria for COVID-19 hyperinflammatory states have been proposed and validated (Table 1) [12▪▪,13▪▪]. In both studies, criteria identified patients at increased risk of prolonged hospitalization, mechanical ventilation, or death. Further studies are needed to better understand the ability of these criteria to discriminate potential benefits of anti-inflammatory therapy. Recently, these criteria have shown an association with hyperinflammation and worse outcomes in patients with rheumatic diseases [14▪].

ANTIRHEUMATIC DRUGS FOR COVID-19

Glucocorticoids

Given the lack of benefits of glucocorticoids in infection-associated syndromes such as influenza, septic shock, and acute respiratory distress syndrome (ARDS), there was significant hesitancy regarding their use in patients with SARS-CoV-2 infection [15]. However, glucocorticoids were used from very early in the pandemic and observational studies showed mixed results [16].

Beneficial effects of dexamethasone for the treatment of severe COVID-19 were initially shown by the RECOVERY trial [17▪]. In this open-label

Table 1. Proposed criteria for COVID-19 hyperinflammatory syndrome

Temple COVID-19 Cytokine Storm Criteria Caricchio *et al.* [12▪▪]	**COVID-19-associated hyperinflammatory syndrome (CHIS) Webb *et al.* [13▪▪]**
Signs/symptoms of COVID-19	Fever > 38°C
RT-PCR for COVID-19	
Ground-glass opacity by HRCT or chest X-ray	
Ferritin > 250 ng/ml	Ferritin ≥ 700 ug/L
CRP > 4.6 mg/dl	IL-6 ≥15 pg/mL, or triglyceride ≥ 150 mg/dL, or CRP ≥ 15 mg/dL
Cluster 1 (one of the following): albumin < 2.8 g/dl, lymphocytes (%) <10.2, neutrophil (absolute) > 11.4 K/mm^3	Neutrophil to lymphocyte ratio ≥ 10, or both hemoglobin ≤ 9.2 g/dL and platelet count ≤ 110 × 10^9 per L
Cluster 2 (one of the following): ALT > 60 U/L, AST > 87 U/L, D-dimer > 4,930 ng/ml, LDH > 416 U/L, Troponin I > 1.09 ng/ml	LDH ≥ 400 U/L or AST ≥ 100 U/L
Cluster 3 (one of the following): Anion gap < 6.8 mmol/L, chloride > 106 mmol/L, potassium >4.9 mmol/L, BUN:creatinine ratio > 29	D-dimer ≥ 1.5 ug/mL

RT-PCR, real time polymerase chain reaction; HRCT, high-resolution chest tomography; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; IL-6, interleukin-6.

adaptive platform randomized controlled trial (RCT), dexamethasone 6 mg (PO or IV) daily for up to 10 days was shown to decrease mortality at 28 days (age-adjusted RR 0.83 [95% CI 0.74–0.92]) when compared to standard of care (SOC). This benefit was observed among patients who required mechanical ventilation (age-adjusted rate ratio (RR) 0.64 [95% CI 0.51–0.91]) or supplemental oxygen (age-adjusted RR 0.82 [95% CI 0.72–0.94]), but showed no benefit, and even concern for possible harm, among patients who did not require respiratory support (age-adjusted RR 1.19 [95% CI 0.91–1.55]). Since the release of RECOVERY, which led to changes in the treatment protocols for patients with COVID-19, several other studies have confirmed these findings using either different formulations (e.g., hydrocortisone, methylprednisolone) or dosing protocols (Table 2) [18–22]. A recent systematic review and meta-analysis of glucocorticoid treatment in COVID-19 showed a benefit of decreased mortality (odds ratio (OR) 0.66 [95% CI 0.52–0.82]) among all patients [23▪].

It is important to note that despite this encouraging data, registry studies of patients with autoimmune disease and baseline glucocorticoid use have shown an increased risk of severe COVID-19 with higher doses of glucocorticoids. Data from the COVID-19 Global Rheumatology Alliance (GRA) showed increased risks of both hospitalization and death in patients with baseline prednisone doses of 10 mg or higher [24,25▪▪]. Limitations to these registries, such as confounding by indication, limit the ability to fully disentangle these associations. However, these data, especially in conjunction with the RECOVERY findings in patients not on ventilatory support, may suggest that timing of intervention might be critical and that use of glucocorticoids could have a different effect depending on the phase of the disease.

Colchicine

Due to its ability to inhibit the NLRP3 inflammasome, leading to suppression of IL-1β, IL-18, and IL-6, colchicine has been proposed as a potential therapeutic for noncritically ill patients with COVID-19 [26]. An Italian cohort study using historical comparators receiving SOC, showed that patients treated with colchicine had a lower risk of death (hazard ratio (HR) 0.15 [95% CI 0.06–0.37]) [27]. Similar results were observed in another Italian single-center propensity score-matched cohort study, showing improving odds of discharge at day 28 and decreased overall mortality (9.1% vs 33.3%, OR 0.20 [95% CI 0.05–0.80]) [28].

An initial open-label RCT from Greece, the Greek Effects of Colchicine in COVID-19 (GRECCO-19) trial, compared colchicine vs SOC in 105 hospitalized COVID-19 patients [29]. The primary outcome, time to deterioration by 2 points in World Health Organization-Clinical Progression Scale (WHO-CPS), was longer in the colchicine arm compared to SOC (20.7 days vs 18.6 days, $P = 0.03$). No difference was observed in the other primary endpoints, including peak high-sensitivity troponin or resolution of CRP levels. Note that more clinically relevant outcomes would have been 30 and 60-day survival as the course of the disease was very heterogeneous and none of these parameters helped predict those at high risk of dying. Most recently, results from the Colchicine for community-treated patients with COVID-19 (COLCORONA) trial, were published [30▪]. In this multicenter RCT of 4488 patients with suspected or confirmed COVID-19 diagnosis, colchicine was administered at a dose of 0.5 mg twice per day for 3 days and later 0.5 mg daily for 27 days vs placebo. In the primary composite outcomes of hospitalization or death, a nonstatistically significant difference was observed (4.7% vs 5.8%, OR 0.79 [95% CI 0.61–1.03]). However, in the prespecified subgroup analysis of 4159 patients with PCR-confirmed COVID-19, a significant decrease in the primary endpoint was observed in patients treated with colchicine (4.6% vs 6.0%, OR 0.75 [95% CI 0.57–0.99]). This yielded a number needed to treat (NNT) of 70 (95% CI 36–1842). Except for a higher incidence of pulmonary embolism in the treatment arm, there were no differences in serious adverse events. The trial was terminated early due to logistical issues therefore potentially underpowering the conclusions. Although its use in high-risk patients might be convenient due to simple route of administration, low cost and relatively safe profile, the potential benefit on mortality is still unclear and will be hopefully clarified by several ongoing trials.

Interleukin-6 inhibitors

The initial associations between IL-6 elevation and COVID-19 severity sparked interest in the use of IL-6 inhibitors for the treatment of severe COVID-19. Initial observational studies showed promising results, and a meta-analysis including 16 studies showed a decreased risk of death (pooled OR 0.57 [95% CI 0.36–0.92]) associated with the use of tocilizumab (TCZ) compared to SOC [31]. Significant heterogeneity among studies was noted. Importantly, several of these studies focused on specific selection criteria that included documented infection with respiratory failure and markers of inflammation (e.g., CRP, ferritin) [32].

Despite encouraging data from observational studies, early RCTs did not confirm these earlier

Table 2. Clinical trials assessing glucocorticoid treatment in patients with COVID-19

Study/Sites	Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
RECOVERY Horby *et al.* [17▪] UK	Hospitalized patients	Suspected or confirmed SARS-CoV-2 infection	Dexamethasone (PO/IV) 6 mg daily up to 10 days ($n=2104$) vs SOC ($n=4321$)	28-day mortality	Reduced mortality with age-adjusted rate ratio 0.83 (95% CI 0.75 to 0.93)	Benefit observed only in patients requiring supplemental oxygen or mechanical ventilation
REMAP-CAP Angus *et al.* [18] North America, Europe, Australia	ICU patients	Suspected or confirmed SARS-CoV-2 infection and respiratory or cardiovascular organ support	IV Hydrocortisone fixed dose 50 mg or 100 mg q6h ($n=143$) vs shock-dependent course 50 mg q6h ($n=152$) vs SOC ($n=108$)	Organ support-free (alive and free of ICU-based respiratory or cardiovascular support) days at 21 days	Superiority in both intervention arms with median organ support-free days of 0 (IQR -1 to 15) vs 0 (IQR -1 to 13) vs 0 (IQR -1 to 11), respectively	Bayesian analysis showing 93% and 80% probability of superiority for fixed-dose and shock-dependent dose, respectively, compared to SOC. Study stopped early due to RECOVERY results
CAPE COVID Dequin *et al.* [20] France	ICU patients	Suspected or confirmed SARS-CoV-2 infection and respiratory failure with at least 1 ventilatory criteria	IV hydrocortisone continuous infusion 200 mg/d for 7 days, then tapered by day 14 ($n=76$) vs SOC ($n=73$)	Treatment failure at day 21, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen	69 treatment failure events, 42.1% with hydrocortisone vs 50.7% with SOC (difference -8.6% [95% CI -24.9 to 7.7%])	Study stopped early by DSMB, pending RECOVERY results. No differences in secondary outcomes including intubation, pronation or use of ECMO
CODEX Tomazini *et al.* [22] Brazil	ICU patients	Suspected or confirmed SARS-CoV-2 infection on mechanical ventilation	IV dexamethasone 20 mg daily for 5 days, then 10 mg daily for 5 days ($n=151$) vs SOC ($n=148$)	MV free-days at day 28	Mean 6.6 ventilator-free days (95% CI 5.0–8.2) vs 4.0 ventilator-free days (95% CI 2.9–5.4) (difference -1.16, [95% CI -1.94 to -0.38)], respectively	No difference in secondary outcomes including all-cause mortality, or adverse events. Trial stopped early given RECOVERY results
GLUCOCOVID Corral-Gudino *et al.* [19] Spain	Hospitalized patients, non-ICU	Suspected or confirmed SARS-CoV-2 with symptoms for at least 7 days, X-ray evidence of pneumonia, abnormal gas exchange and evidence of systemic inflammatory response	IV methylprednisolone 40 mg BID for 3 days, then 20 mg BID for 3 days ($n=56$) vs SOC ($n=29$)	Composite outcomes of death, admission to ICU, or requirement of noninvasive ventilation	Relative risk 0.68 (95% CI, 0.37 to 1.26)	22 patients in the intervention arm were allocated by the treating physicians. 21 patients received other anti-inflammatory treatments

Table 2 (*Continued*)

Study/Sites	Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
METCOVID Jeronimo *et al.* [72] Brazil	Hospitalized patients	Suspected SARS-CoV-2 infection and SpO2 ≤ 94% on room air OR under mechanical ventilation	IV methylprednisolone 0.5 mg/kg BID for 5 days ($n = 194$) vs SOC ($n = 199$)	28-day mortality	Deaths 37.1% with methylprednisolone vs 38.2% with SOC, HR 0.92 (95% CI 0.67 to 1.28)	Mortality reduced in subgroup analysis of patients > 60 years (HR 0.63 [95% CI 0.41–0.98])
Ranjbar *et al.* [21] Iran	Hospitalized patients	Confirmed SARS-CoV-2 infection and SpO2 < 92% on room air	IV methylprednisolone 2 mg/kg/d and tapering dose every 5 days ($n = 47$) or IV dexamethasone 6 mg/d for 10 days ($n = 46$)	28 day mortality and clinical status at days 5 and 10 (WHO ordinal scale)	23 deaths, 18.6% methylprednisolone vs 37.5% dexamethasone ($P = 0.08$)	For methylprednisolone treated patients, improved clinical status seen at days 5 and 10 ($P = 0.002$ and $P = 0.001$, respectively)

IV, intravenous; PO, oral; SOC, standard of care; ICU, intensive care unit; IQR, interquartile range; SpO2, oxygen saturation; DSMB, data safety monitoring board; CI, confidence interval; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; WHO, World Health Organization.

observations (Table 3). The CORIMUNO-19 and COVACTA trials, which did not include inflammatory criteria for inclusion, failed to meet their primary endpoints [33,34]. The RCT-TCZ-COVID-19 and BACC BAY trials, which did include inflammatory criteria for inclusion, were potentially underpowered due to early stoppage or an unexpected low number of events, respectively [35,36]. More recent and larger RCTs, where most patients enrolled were also receiving background glucocorticoid treatment, have shown more positive results with regards to the use of IL-6 inhibition in severe COVID-19. The EMPACTA trial, which included 389 patients, showed a 44% decreased risk (HR 0.56 [95% CI 0.33–0.97]) of the composite outcomes of mechanical ventilation or death associated with the use of TCZ [37]. No improvement in all-cause death was observed. In the REMAP-CAP trial, that randomized patients to either TCZ, sarilumab or placebo, an improvement in organ support-free days and increased survival at 90 days were seen for both IL-6 inhibitors [38▪].

These results have been also confirmed by more recent trials including the RECOVERY trial. In the TCZ intervention arm from the RECOVERY adaptive platform, where 4116 patients were randomized to either TCZ or SOC, the risk of all-cause death was lower in patients treated with TCZ (adjusted RR 0.85 [95% CI 0.76–0.94]) [39▪▪]. Decrease in time to discharge and composite of mechanical ventilation and death was also lower in the intervention arm. These new findings, therefore, suggest benefits from the use of IL-6 inhibition, in addition to background glucocorticoid treatment, in patients with elevated markers of inflammation.

Interleukin-1 inhibitors

Transcriptomic analysis of whole blood of COVID-19 patients showed increasing expression IL-1α and IL-1β prior to the nadir of respiratory function, unlike other proinflammatory cytokines [40]. Also, given the clinical similarities between cytokine storm syndromes and COVID-19 hyperinflammation, use of IL-1 inhibitors for the treatment of severe COVID-19 was considered early in the pandemic [41–44].

Early case series and cohort studies suggested improvement in clinical outcomes of severe COVID-19 with anakinra, an IL-1 receptor antagonist. In a meta-analysis of two large cohort studies, anakinra was associated with a lower risk of mortality (pooled HR 0.2 [95% CI 0.1–0.4]) [16]. Despite these encouraging results, RCTs have not supported these observations (Table 4). The CORIMUNO-ANA-1 trial, a French multicenter open-label study, randomized patients to intravenous anakinra (200 mg BID on days 1–3, 100 mg BID on day 4, and 100 mg once on day 5)

Table 3. Studies assessing Interleukin-6 inhibitor treatment in patients with COVID-19

Study/Sites	Design/Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
SARI-RAF Della-Torre *et al.* [32] Italy	Open-label, not randomized/ Hospitalized	Confirmed SARS-CoV-2 infection with bilateral pneumonia with SpO2 $\leq$ 92% or PaFiO2 $\leq$ 300 mmHg and hyperinflammation (elevated LDH and one of the following: CRP $\geq$ 100 mg/l, IL-6 $\geq$ 40 pg/ml, ferritin $\geq$ 900 ng/ml)	SAR 400 mg once ($n=28$) vs SOC ($n=28$)	Clinical improvement (WHO-CPS) and mortality at 28 days	No difference in clinical improvement (61% vs 64%, $P=0.94$) or mortality (7% vs 18%, $P=0.21$)	Median time to clinical improvement shorter in sarilumab treated patients (10 days vs 24 days, $P=0.01$). SOC includes antiviral, hydroxychloroquine and antibiotic therapy.
CORIMUNO-19 Hermine *et al.* [33] France	Open-label RCT/ Hospitalized non-ICU patients	Confirmed SARS-CoV-2 with moderate, severe or critical pneumonia (O2 > 3L/min) (intubation excluded)	IV TCZ 8 mg/kg single dose ($n=64$) vs SOC ($n=67$). Option of second dose at 72h	Score > 5 on WHO-CPS at day 4 and intubation or death at day 14	No difference in WHO-CPS (ARD -9.0% [90 CrI -21.0 to 3.1]) On day 14, 24% with TCZ vs 36% with SOC (HR 0.58 [90% CrI 0.33–1.00])	No difference on intubation or death at day 28. 17% of patients with background glucocorticoids.
RCT-TCZ-COVID-19 Salvarani *et al.* [36] Italy	Open-label RCT/ Hospitalized non-ICU patients	Confirmed SARS-CoV-2 with PAFiO2 200–300 mmHg and inflammatory phenotype: fever (> 38°C) last 2 days and/ or CRP $\geq$ 10 mg/dL or CRP doubled since admission	IV TCZ 8 mg/kg single dose ($n=60$) vs SOC ($n=66$). Option of second dose at 12h	Composite outcome of clinical worsening including MV, death or PaFIO2 < 150 mmHg	28.3% with TCZ vs 27.0% in SOC (RR 1.05 [95% CI 0.59–1.86])	Stopped early due to futility on interim analysis.
BACC BAY Stone *et al.* [35] US	Double-blinded RCT/ Hospitalized non-ICU patients	Confirmed SARS-CoV-2 with at least 2 of the following: fever (> 38°C) within 72h of enrollment, pulmonary infiltrates, supplementary oxygen to maintain SpO2 $\geq$ 92%; and one of the following: CRP > 50 mg/L, ferritin > 500 ng/ml, D-dimer > 1000 ng/ml, LDH > 250 U/L	IV TCZ 8 mg/kg single dose ($n=161$) vs SOC ($n=82$)	MV or death (time-to-event)	17 events with TCZ vs 10 events in SOC (HR 0.83 [95% CI 0.38–1.81])	No benefit for secondary outcome of clinical worsening (HR 1.11 [95% CI 0.59–2.10) Possibly underpowered due to the low number of events.

Table 3 (*Continued*)

Study/Sites	Design/Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
TOCIBRAS Veiga *et al.* [73] Brazil	Open-label RCT/ Hospitalized patients	Confirmed SARS-CoV-2 with supplemental oxygen or mechanical ventilation and at least two of the following: D-dimer > 1000 ng/ml, CRP > 5 mg/dl, ferritin > 300 ug/L, or LDG > ULN	IV TCZ 8 mg/kg single dose ($n=65$) vs SOC ($n=64$)	Clinical status (ordinal scale) at day 15	Patients on MV or deaths: 28% with TCZ vs 20% with SOC (OR 1.54 [95% CI 0.66–3.66])	No differences in 28 day or in-hospital mortality. 71% of patients on glucocorticoids.
EMPACTA Salama *et al.* [37] North and South America	Double-blinded RCT/ Hospitalized patients non-ICU	Confirmed SARS-CoV-2 receiving supplemental oxygen (noninvasive or invasive ventilation excluded)	IV TCZ 8 mg single dose ($n=259$) vs SOC ($n=128$). Option for second dose 8–24h	MV or death at day 28	12% with TCZ vs 19.3% with SOC (HR 0.56 [95% CI 0.33–0.97])	No improvement on death from any cause. Clinical failure assessed in time-to-event analysis favored TCZ. Majority of patients on glucocorticoids (>80%) and antiviral therapy (>70%).
COVACTA Rosas *et al.* [34] North America and Europe	Double -blind RCT/ Hospitalized patients	Confirmed SARS-CoV-2 with SpO2 $\leq$ 93% or PaFIO2 < 300 mmHg	IV TCZ 8 mg single dose ($n=301$) vs SOC ($n=151$). Option for second dose 8–24h	Clinical status (7-category ordinal scale) at day 28	Median value for clinical status on ordinal scale 1.0 with TCZ vs 2.0 with SOC (between group difference -1.0 [95% CI -2.5 to 0)	No difference in mortality at day 28. 37% on invasive MV at baseline.
REMAP-CAP Gordon *et al.* [38▪] Multiple countries	Open-label RCT/ICU patients	Suspected or confirmed SARS-CoV-2 on respiratory or cardiovascular organ support	IV TCZ 8 mg/kg single-dose ($n=353$) or IV SAR 400 mg ($n=48$) vs SOC ($n=402$)	Organ support-free days at day 21	Median number of organ support-free days 10 with TCZ (aOR 1.64 [95% CrI 1.25 to 2.14] for TCZ), 11 with SAR (aOR 1.76 [95% CrI 1.17–2.91]) vs 0 with SOC	Improved survival at 90 days for TCZ or SAR treated patients. > 80% of patients on glucocorticoids.

Table 3 (*Continued*)

Study/Sites	Design/Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
Lescure *et al.* [74] Multiple countries	Double-blind RCT/ Hospitalized patients	Confirmed SARS-CoV-2 with severe (oxygen supplementation) or critical (noninvasive and invasive ventilation) disease	IV SAR 400 mg single dose ($n=173$) vs IV SAR 200 mg ($n=161$) vs SOC ($n=86$). Option for a second dose 24–48h	Time to clinical improvement of $\geq$ 2 points (7-category ordinal scale)	Median time to improvement 10 days with SAR 400 mg (HR 1.14 [95% CI 0.83–1.54]) vs 10 days with SAR 200 mg (HR 1.03 [95% CI 0.75–1.40]) vs 12 days with SOC	No difference in survival.
COVINTOC Soin *et al.* [75] India	Open-label RCT/ Hospitalized	Confirmed SARS-CoV-2 with moderate (RR 15–30/min and SpO2 90–94%) or severe (RR $>$ 30/min and SpO2 $<$ 90%) or ARDS or septic shock	IV TCZ 6 mg/kg ($n=90$) vs SOC ($n=90$). Option for second dose at 12h to 7d	Progression from moderate to severe, or severe to death up to day 14	Progression in 9% with TCZ vs 13% with SOC (mean difference -3.71 [95% CI -18.23 to 11.19])	91% of patients on glucocorticoids.
RECOVERY Abani *et al.* [39▪▪] UK	Open-label RCT/ Hospitalized patients	Suspected or confirmed SARS-CoV-2 with hypoxia (SpO2 $<$ 92%) and CRP $\geq$ 75 mg/L)	IV TCZ 400–800 mg ($n=2022$) vs SOC ($n=2094$)	All-cause death at day 28	31% with TCZ vs 35% with SOC (aRR 0.85 [95% CI 0.76–0.94])	Decrease in time to discharge and composite of MV or death (in non-MV patients at baseline). 80% patients on glucocorticoids.

IV, intravenous; SOC, standard of care; ICU, intensive care unit; IQR, interquartile range; SpO2, oxygen saturation; PaFIO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; TCZ, tocilizumab; SAR, sarilumab; CI, confidence interval; CrI, credible interval; HR, hazard ratio; OR, odds ratio; aRR, adjusted relative risk; WHO-CPS, World Health Organization Clinical Progression Scale; CRP, C reactive protein; LDH, lactate dehydrogenase; RR, respiratory rate; ARDS, acute respiratory distress syndrome.

Table 4. Studies assessing interleukin-1 inhibitor treatment in patients with COVID-19

Study/Sites	Design/ Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
CORIMUNO-ANA-1 Bureau *et al.* [45▪▪] France	RCT/Hospitalized patients non-ICU	Confirmed SARS-CoV-2 infection with mild-moderate, severe or critical pneumonia and CRP > 25 mg/L	IV Anakinra 200 mg BID on day 1-3, then 100 mg BID day 4 and 100 mg day 5 ($n=59$) vs SOC ($n=57$) Additional doses given if no improvement after day 4	Score > 5 on WHO-CPS at day 4 or composite outcome of MV or death at day 14	WHO-CPS >5 at day 4: 36% with anakinra vs 38% with SOC (ARD -2.5% [90% CrI -17.1 to 12.0]) MV or death at day 14: 47% with anakinra vs 51% with SOC (HR 0.97 [90% CrI 0.62–1.52])	Study stopped early by recommendation of DSMB.
SAVE Kyriazopoulou *et al.* [47] Greece	Open-label nonrandomized with parallel controls/ Hospitalized patients non-ICU	Confirmed SARS-CoV-2 infection, imaging consistent with pneumonia and plasma suPAR levels > 6 ng/ml	SC anakinra 100 mg daily for 10 days ($n=130$) vs SOC ($n=179$)	Severe respiratory failure at day 14	22.3% with anakinra vs 59.2% with SOC (HR 0.30 [95% CI 0.20–0.46])	Parallel controls chosen by propensity-score matching. Decrease mortality.
OMA-COVID-19 Balkhair *et al.* [76] Oman	Prospective, open-label interventional study/ Hospitalized patients	Confirmed SARS-CoV-2 infection, imaging consistent with bilateral pneumonia, and at least one of the following: RR >30/min and SpO2 < 90% on RA, SpO2 ≤ 93% on oxygen ≥ 6L/ min, ARDS.	SC anakinra 100 mg BID for 3 days, then 100 mg daily for 7 days ($n=45$) vs SOC ($n=24$)	MV and in-hospital death	MV: 31% with anakinra vs 75% with SOC ($P<0.001$) In-hospital death: 29% with anakinra vs 46% SOC ($P=0.082$)	Historical controls. 60% on glucocorticoids.
CAN-COVID *Press release* [48] US and Europe	RCT/Hospitalized patients non-ICU	Confirmed SARS-CoV-2 infection, imaging consistent with pneumonia, SpO2 ≤ 93% on RA or PaFiO2 < 300 mmHg, and CRP ≥ 20 mg/L or ferritin ≥ 600 ug/L	Canakinumab weight-bases single dose vs SOC	Survival without MV at day 28	88% with canakinumab vs 85.7% with SOC ($P=0.29$)	No difference in mortality. Interim analysis, pending final publication.

IV, intravenous; SOC, standard of care; ICU, intensive care unit; SpO2, oxygen saturation; suPAR, soluble urokinase plasminogen activator receptor; CI, confidence interval; CrI, credible interval; HR, hazard ratio; OR, odds ratio; ARD, absolute risk difference; ARDS, acute respiratory distress syndrome; WHO-CPS, World Health Organization Clinical Progression Scale; CRP, C reactive protein.

or to SOC in patients with COVID-19 requiring at least 3L/min O_2 and a CRP greater than 25 mg/L [45▪▪]. The study was stopped early by recommendation of the data safety monitoring board, and no differences were found in the primary outcomes of improvement in clinical status at day 4 or need for mechanical ventilation or death at day 14. The Anakinra for COVID-19 Respiratory Symptoms (ANACONDA) study was also stopped early due to concern for worse outcomes in the intervention arm [46]. Results of this study are not available. Interestingly, a Greek open-label interventional study that allocated treatment with anakinra to patients with COVID-19 and elevated levels of soluble urokinase plasminogen activator receptor (suPAR) showed a decrease in mechanical ventilation in patients treated with anakinra [47].

Treatment with canakinumab, an IL- β inhibitor, has also been assessed in small case series and in larger studies. The CAN-COVID study, a phase 3 trial, randomized patients to either canakinumab or SOC [48]. Although results of the study have not been published, a press release in November 2020 announced that the study did not achieve its primary endpoint of improvement in survival without mechanical ventilation at day 28. Currently, the role of IL-1 inhibitors for the treatment of COVID-19 is not clear, and hopefully ongoing phase 3 clinical trials will better clarify this point.

Tumor necrosis factor α inhibitors

Based on observations of elevated TNF-α levels in patients with severe COVID-19, there is growing interest regarding the use of TNF-inhibitors for the treatment of COVID-19 [49]. In fact, a role for TNF inhibition in animal models of other viral lung diseases such as influenza has been proposed [50]. These mechanistic observations have also been reinforced by lower odds of severe COVID-19 in patients on baseline TNF-inhibitors such as rheumatic and inflammatory bowel disease patients [51▪]. Currently, five ongoing trials utilizing infliximab in hospitalized COVID-19 patients and one using adalimumab in ambulatory COVID-19 patients are ongoing (Table 5).

Table 5. Ongoing studies assessing tumor necrosis factor (TNF)-α inhibitor treatment in patients with COVID-19

Drug	Clinical Trials.gov Identifier	Design/Setting	Intervention	Inclusion criteria	Primary outcome
Infliximab	NCT04425538	Single group assignment/ hospitalized patients non-ICU	IV Infliximab 5 mg/kg. Option for second dose 7–21 days	Confirmed SARS-CoV-2 infection, pneumonia evidenced by imaging and at least one of the following: RR ≥ 30/min, SpO2 ≤ 93% on RA, PaFIO2 < 300, worsening lung involvement	Time to improvement in oxygenation
Infliximab	NCT04734678	Cohort/Hospitalized patients non-ICU	IV TCZ 400 mg single dose vs IV TCZ 400 mg single dose + IV Infliximab 5 mg/kg/d for 2 doses	Confirmed SARS-CoV-2 infection, pneumonia evidenced by imaging, hyperinflammation (either CRP ≥ 100 mg/L, ferritin ≥ 900 ng/ml with LDH > 220 U/L) and at least one of the following: RR ≥ 30/ min, SpO2 ≤ 93% on RA, PaFiO2 < 300, involvement	Clinical status improvement (6 category scale)
Infliximab ACTIV-1 IM	NCT04593940	RCT/Hospitalized patients	IV Infliximab 5 mg/kg single dose vs SOC	Confirmed SARS-CoV-2 infection with ongoing illness and at least one of the following: radiographic infiltrates, SpO2 ≤ 94% RA, supplemental oxygen requirement, MV or ECMO	Time to recovery by day 29
Infliximab RECOVERY	NCT04381936	RCT/Hospitalized	IV infliximab 5 mg/kg single dose vs SOC	Suspected or confirmed SARS-CoV-2 infection	All-cause mortality
Adalimumab COMBAAT	NCT04705844	RCT/ Nonhospitalized patients	SC Adalimumab 160 mg (40 mg, 4 doses) vs SOC	Confirmed SARS-CoV-2, COVID-19 related symptoms, SpO2 > 93%, and at least one of the following: CRP > 50 mg/L, lymphopenia < 1.5 x 10^9/L, neutrophilia > 7.5 x 10^9/L	Rate of progression to severe disease or death

IV, intravenous; SC, subcutaneous; SOC, standard of care; ICU, intensive care unit; SpO2, oxygen saturation; PaFIO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; TCZ, tocilizumab; CRP, C reactive protein; LDH, lactate dehydrogenase; RR, respiratory rate; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

Janus kinase inhibitors

For the treatment of COVID-19 infection, JAK inhibitors have two proposed mechanisms of action: inhibition of viral entry to cells through disruption of AAK1 and decreased signaling of pro-inflammatory cytokines, such as IL-2, IL-6, and IFN-γ, through inhibition of the JAK-STAT pathway [9,52]. A meta-analysis of observational studies using baricitinib and ruxolitinib for the treatment of COVID-19 showed lower odds of mortality, ICU admission, and higher odds of discharge associated with treatment. It is important to note that studies included were observational and presented significant heterogeneity [53]. The Adaptive COVID-19 Treatment Trial 2 was the first published double-blind RCT comparing baricitinib against placebo (with background remdesivir) [54▪▪]. In this trial of 1033 hospitalized patients, those treated with baricitinib had a shorter time to recovery (7 vs 8 days, $P = 0.03$) and higher odds of clinical improvement (OR 1.3 [95% CI 1.0–1.6]). A nonsignificant trend toward lower mortality at day 28 was also noted. Most recently, the preprint results of a large global RCT of 1525 hospitalized patients showed no difference in its primary outcome of reduction of disease progression (OR 0.86 [95% CI 0.67–10.8]) [55]. However, a 38.2% reduction in mortality was observed in all prespecified groups. In both trials, no difference in venous thromboembolic events was noted.

Interestingly, similar to glucocorticoids, baseline use of JAK inhibitors has been associated with worse COVID-19 outcomes. A recent analysis of a large cohort of rheumatoid arthritis (RA) patients showed that use of JAK inhibitors was associated with a higher risk of worse COVID-19 severity (OR 1.52 [95% CI 1.02–2.28]) compared to TNF inhibitors [56▪]. These findings may be associated with inhibition of the interferon pathway which is necessary for the clearance of viral infections, and may also speak to the importance of timing of the intervention. Results from the ongoing trial will provide further information regarding the use of these drugs for the treatment of COVID-19 (Table 6).

Granulocyte-monocyte colony-stimulating factor inhibitors

Granulocyte-monocyte colony stimulating factor (GM-CSF) inhibiting therapies are currently being studied for the treatment of rheumatic diseases such as RA and giant cell arteritis [57,58]. GM-CSF has been associated with severe COVID-19, and elevated levels have been associated with markers of endothelial injury and thrombosis [59]. Bronchoalveolar lavage fluid analysis from patients with severe COVID-19 has shown high levels of Th-17 cells associated with an overexpression of GM-CSF and IL-17A [60].

An initial study with lenzilumab (600 mg IV for three doses) in 12 patients with severe COVID-19 showed a faster improvement in clinical outcomes when compared to a matched control cohort receiving SOC (5 days vs 11 days, $P = 0.06$) [61]. Although clinical improvement was similar in both groups, the proportion of patients with ARDS was also reduced with lenzilumab treatment. The first published RCT assessing the use of a GM-CSF inhibitor, mavrilimumab, randomized patients to mavrilimumab vs SOC [62]. The Mavrilumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID) study included hospitalized patients with COVID-19 pneumonia, hypoxemia, and CRP > 5 mg/dl. The primary outcome of survival without supplementary oxygen at day 14 was not different between the two groups (57% vs 47%, OR 1.48 [95% CI 0.43–5.16]. The results of this study were underpowered due to early termination after slow recruitment. Preprint results of two larger trials, LIVE-AIR (with lenzilumab) and OSCAR (otilimab), and ongoing studies will further clarify the role of GM-CSF inhibitors as treatment options for severe COVID-19 [63,64].

Anticomplement therapy

Complement activation has been shown to play a central role in the pathophysiology of both ARDS and macrovascular thrombosis. Endothelial injury secondary to activation of anaphylatoxins (C3a, C4a, and C5a) is a key component in the pathway of both of these complications [65▪]. Even more so, increased complement activation seems to be a distinctive feature of severe COVID-19 as shown by significant elevation of circulating markers of complement activation when compared to patients with other critical conditions, including influenza infection [66].

Use of eculizumab, a C5 inhibitor, for the treatment of severe COVID-19 has been described in several case reports. Eculizumab (900 mg, 2 doses) in addition to SOC was associated with recovery of four patients with severe COVID-19 [67]. In a nonrandomized controlled study of 80 patients with severe COVID-19, 35 patients treated with eculizumab vs 45 patients receiving SOC, patients treated with eculizumab had a higher survival at day 15 (82.9% vs 62.2%, $P = 0.04$) [68]. A phase 2 trial of IFX-1, a C5a inhibitor, showed no difference in its primary outcome of percentage change in PaFIO2, but showed a nonsignificant trend toward improved survival and decreased pulmonary embolisms [69]. Further knowledge of anticomplement therapies,

Table 6. Ongoing phase 3 or 4 randomized controlled trials assessing Janus Kinase inhibitor treatment in patients with COVID-19

Clinical Trials.gov Identifier/Study	Design	Intervention	Inclusion criteria	Primary outcome
Baricitinib				
NCT04421027	RCT/Hospitalized non-ICU	BARI 4 mg PO daily vs SOC	Confirmed SARS-CoV-2 infection, supplemental oxygen requirement, and at least one inflammatory marker > ULN: CRP, d-dimer, LDH, ferritin	Death or requirement of noninvasive ventilation/ HFNC or MV
NCT04358614	RCT/Hospitalized patients	BARI 4 mg PO daily for 14 d + antiviral vs antiviral	Confirmed SARS-CoV-2, radiographic infiltrates, SpO2 > 92%, PaFIO2 > 100–300 mmHg	Safety in terms of serious and nonserious adverse events
NCT04832880 AMMURAVID	RCT/ Hospitalized patients non-ICU	Dexamethasone (SOC) vs Remdesivir + SOC vs BARI 4 mg PO for 10 days + SOC vs Remdesivir + BARI + SOC	Confirmed SARS-CoV-2 infection, <10 days of symptom onset and Temple COVID-19 CS criteria	Composite outcome of Very severe respiratory failure (PaFIO2 < 150 mmHg) or mortality
NCT04693026	RCT/ ICU patients	Remdesivir + BARI 4 mg PO 14 days vs Remdesivir + TCZ	Confirmed SARS-CoV-2 + admission ICU	Time to clinical improvement
NCT04640168 ACTT-4	RCT/Hospitalized patients non-ICU	Remdesivir + BARI 4 mg PO 14 days vs Remdesivir + Dexamethasone	Confirmed SARS-CoV-2 + new oxygen requirement within past 7 days	Survival without MV and death
NCT04390464 TACTIC-R	RCT/Hospitalized patients non-ICU	BARI 4 mg PO 14 days vs Ravulizumab vs SOC	Suspected SARS-CoV-2 infection and severe disease	Time of incidence to composite endpoint of death, MV, ECMO, CV organ support or renal failure
NCT04890626	RCT/ Hospitalized patients	BARI + dexamethasone vs dexamethasone (SOC)	Confirmed SARS-CoV-2 infection	Death at day 28
NCT04891133 EU SolidAct	RCT/Hospitalized patients	BARI 4 mg PO 14 days + SOC	Confirmed SARS-CoV-2 infection + moderate-severe disease	Death at day 60
NCT04381936 RECOVERY	Open label-RCT/ Hospitalized patients	BARI 4 mg PO 10 days + SOC	Suspected or confirmed SARS-CoV-2 infection	All-cause mortality at day 28
Ruxolitinib				
NCT04424056 INFLAMMACOV	Open-label RCT/ Hospitalized patients	Ruxolitinib +/- TCZ or Anakinra vs SOC	Confirmed SARS-CoV-2 infection and hypoxemic pneumonia with CRP > 150 ng/ml or PAFIO2 < 300 or PaFIO2 < 200 with another organ failure	Ventilation free days at day 28

RCT, randomized controlled trial; BARI, baricitinib; SOC, standard of care; ICU, intensive care unit; SpO2, oxygen saturation; PaFIO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; TCZ, tocilizumab; CRP, C reactive protein; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CV, cardiovascular.

including identification of biomarkers of patients who would benefit from these, are needed.

CONCLUSION

The unprecedented challenge of the global COVID-19 pandemic has rightfully monopolized the attention of the entire medical field. The hyperinflammatory features of severe COVID-19, somehow resembling those of rheumatic and cytokine storm syndromes, have placed both rheumatologists and the immunomodulatory medications used for the treatment of rheumatic diseases in a unique position. The successful use of glucocorticoids such as dexamethasone for the

treatment of COVID-19 has shown the benefits of immunomodulation. Interestingly observations such as those from the RECOVERY trial and large registries of patients with baseline glucocorticoid use (similar to JAK inhibitors), highlight the importance of timing of intervention. Even more so, studies have also shown the role of host characteristics, such as inborn errors in type I IFN immunity, therefore highlighting the need to better characterize patients at risk of COVID-19 hyperinflammation and potentially those who would benefit the most from immunomodulatory interventions [70▪,71▪▪].

Challenges to research during the COVID-19 pandemic have also left several valuable lessons that should be incorporated in future scenarios. As shown in this review, discordant results of trials assessing the same drug could be potentially explained by lack of uniform selection criteria, changes in definitions of SOC or changes in timing, dosages or duration of interventions. Understandably, the dynamic nature of the pandemic and knowledge generated has led to some of these limitations. However, coordinated efforts such as the RECOVERY adaptive trial platform have led to invaluable knowledge.

Although glucocorticoids have an established role in the treatment of severe COVID-19, other immunomodulatory therapies such as JAK inhibitors, particularly baricitinib, and IL-6 might require further studies despite some encouraging results. Particularly, studies are needed to better identify patients who would benefit from these interventions. Hopefully, ongoing RCTs or studies utilizing proposed COVID-19 hyperinflammatory phenotypic criteria will shed some light on this matter as well the role of other DMARDs such as IL-1, GM-CSF and complement inhibitors. Although approved vaccines are helping to mitigate the pandemic, the need to identify better treatment options for patients with severe COVID-19 and complications such as COVID-19 hyperinflammation remains crucial.

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