Immunomodulation as Treatment for Severe COVID-19: ***a systematic review of current modalities and future directions***

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Summary: Evidence supports an acute viral process followed by an immune dysregulation phase in severe COVID-19, associated with inadequate early type I interferon response and imbalanced innate and adaptive immunity. We review clinical data available for various immunomodulatory therapies.

Abstract

In SARS-CoV-2 infection, the viral load peaks early setting off a cascade of immune dysregulation that persists well after viral clearance. Severe COVID-19 is marked by aberrant innate and adaptive immune responses with an abnormal cytokine profile and a prolonged illness course with multisystem organ dysfunction. Antiviral treatments have yet to show benefit later in critical illness. Taken together, this raises the concern that a purely antiviral treatment approach may be insufficient. A number of immunomodulatory strategies are being tested, including corticosteroids, cytokine and anti-cytokine therapies, small molecule inhibitors, and cellular therapeutics. The only drug to date to show a mortality benefit for COVID-19 in a randomized control trial is dexamethasone, but there remains uncertainty about which patients may benefit most and longer-term complications including secondary infections. Here we review the immune dysregulation of severe COVID-19, the existing data behind various immunomodulatory strategies, and consider future directions of study.

Key words: COVID-19, SARS-CoV-2, immunomodulation, hyperinflammatory, cytokine storm, treatments

Introduction

Infection with severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) results in a wide spectrum of disease. Among individuals with symptomatic coronavirus disease 2019 (COVID-19), approximately 15-20% are estimated to develop severe presentations requiring supplemental oxygen, including up to 5% who may develop critical illness.[2] Infection fatality rates are population and age dependent, with very low rates for children and young adults but mortality rates >25% for individuals over age 90.[3] Areas with rapid surges of infections, associated with delayed access to care, may have higher fatality rates, as was found in Spain and New York City.[4, 5] The explanation for the profound differences in disease severity stratified by age are unknown and likely multifactorial. Current theories include possible increased likelihood of cross-protective cellular immune response from recent infection with common human coronaviruses and age-related changes in immunity, including decreased availability of naïve T cells to respond to new viral antigens in older adults.[6-8] Autopsy studies demonstrate that the primary pulmonary pathology is diffuse alveolar damage, with micro and macrovascular thrombosis.[9]

Symptomatic patients typically develop mild symptoms during an acute viral phase although a subset of patients will progress to severe disease that can last weeks and often requires hospitalization.[10-12] This severe stage is typically marked by immune dysregulation and abnormal inflammatory markers (Figure 1). Higher upper respiratory tract viral loads are associated with more severe presentations.[13, 14] Numerous therapeutic agents are currently under investigation for treatment of COVID-19. During the early phase of the pandemic, many agents were given off label or in the context of randomized controlled trials (RCTs). While we will review randomized and non-randomized series here, it is important to note that only data from high quality RCTs should change practice in the next phase of the pandemic.

The main therapeutic strategies are direct antiviral and immunomodulatory approaches. To date, remdesivir, a nucleoside analogue that targets the viral RNA dependent RNA polymerase, has the most

supportive data. It has shown efficacy when given early to rhesus macaques as well as improvement in time to recovery in a large RCT compared to placebo called the Adaptive COVID-19 Treatment Trial (ACTT)-1.[15-17] There was a suggestion of a mortality benefit in patients on supplemental oxygen but not in the ICU, with no or minimal survival benefit seen for those with critical disease.[17-19] A challenge to antiviral therapy for COVID-19 is that patients with severe disease tend to present after 5-7 days of symptom when viral loads are declining.[20, 21]

The only agent yet to show a mortality benefit for COVID-19 is dexamethasone. In a large open label, UK-based RCT called RECOVERY, over 6000 patients were randomized in a 1:2 fashion to dexamethasone or standard of care, with a lower mortality recorded in the dexamethasone group (22.9% vs 25.7%, $p<0.001$). The benefit was largest in those who were mechanically ventilated and there was no benefit among those without hypoxemia. Additionally, a mortality benefit was seen for those who received dexamethasone after 7 days of symptoms, but not if they received the agent before that time.[22] That remdesivir has not shown a significant benefit in critically ill patients and that the mortality benefit with dexamethasone is strongest in this group (and after 7 days of symptoms) further suggests a viral followed by an immune dysregulation phase.

That immunomodulation might impact COVID-19 outcomes is also suggested from some epidemiologic studies. While confounding and indication bias need to be considered, rheumatologists and inflammatory bowel specialists report early data suggestive of a lower incidence of severe COVID-19 for patients prescribed TNF-α inhibitors compared with similar cohorts on chronic steroids.[23, 24]

[Figure 1]

Methods

We searched for English-language titles, abstracts and relevant articles from LitCovid, an electronic literature hub for COVID-19-related articles indexed on PubMed from January 2020 through October 21, 2020 using terms including corticosteroids, methylprednisolone, dexamethasone, tocilizumab, sarilumab, ruxolitinib, baricitinib, anakinra or interferons. All RCTs were included, regardless of study size. Non-randomized studies of at least 50 individuals treated with corticosteroids or tocilizumab were included. For other agents, reports were included if ≥20 individuals received the treatment. When no peer reviewed data were available, press releases and preprints for major were included.

Accumulating Evidence for an Immune Dysregulation Contributing to Severe COVID-19

Early descriptions of patients with severe COVID-19 reported marked derangements in inflammatory markers, including elevated levels of interleukin-6 (IL-6), ferritin, and C-reactive protein (CRP) each associated with severe outcomes.[25, 26] For example, high IL-6 levels are associated with progression to mechanical ventilation,[27] elevated SARS-CoV-2 viremia and longer viral RNA shedding.[28-30] Detailed cytokine profiling has noted significant differences between survivors and non-survivors in other markers of inflammation, including IL-2 receptor, IL-8, IL-10 and TNF-α.[31] The cytokine profile and clinical features of the second phase of severe COVID-19 illness have similarities to cytokine release syndrome (CRS) associated with chimeric antigen receptor (CAR)-T cell therapy. In both clinical scenarios, IL-6, circulating at abnormally high levels may result in a signaling cascade leading to vascular permeability and multisystem organ dysfunction.[32] In CRS, targeting the IL-6 axis is lifesaving,[33] and led to early interest in IL-6 receptor inhibition as a possible treatment for severe COVID-19. More recently, several studies have reported that while certain cytokine are elevated in severe COVID-19, they are less elevated than other conditions including bacterial sepsis or non-COVID-19

acute respiratory distress syndrome.[34, 35] Therefore it has become clear that severe or critical COVID-19 is not a true cytokine storm state.

The picture that is emerging is far more complex, with dysfunction of both the innate and adaptive immune system contributing to severe COVID-19. Transcriptional changes in host cells after SARS-CoV-2 infection include upregulation of cytokines such as IL-6 and IL-1 receptor antagonist as well as reduced interferon expression. There is also induction of other cytokines and chemokines, including CCL2 and CCL8 (which recruit macrophages) and CXCL2 and CXCL8 (which recruit neutrophils).[36] This "imbalanced host response" is a hallmark of COVID-19 as the proinflammatory state starts within days after infection and persists long after viral clearance.[36] This cytokine milieu recruits and activates neutrophils, macrophages, and T-lymphocytes.[37] In another study of critically ill patients with COVID-19, circulating CD8+ T-lymphocytes showed significant reductions in cytokines and NK cells had decreased intracellular expression of antiviral cytotoxic mediators granzyme A and perforin consistent with an "exhausted phenotype."[38]

The type I interferon signaling pathway has emerged as likely playing a central role in COVID-19 pathogenesis. Inborn errors of the type I interferon pathway and auto-antibodies to the against type I interferons are present (and over-represented) in some patients with severe COVID-19.[39, 40] Additionally, the SARS-CoV-2 genome encodes structural and nonstructural proteins that antagonize type I interferons[41] At the same time, interferon-beta inhibits SARS-CoV-2 replication.[42] Attenuation of the type I interferon response is associated with inhibition of STAT1 and activation of STAT3 signaling, which has myriad downstream effects, including induction of various inflammatory cytokines and dampening an effective T cell response.[43]

The adaptive immune response to SARS-CoV-2 infection is also under intense study. A coordinated early adaptive immune response with generation of SARS-CoV-2 specific CD4+ and CD8+ T cells and neutralizing antibodies is associated with less severe outcomes.[8] CXCL10 has been found to

have a strong negative correlation with SARS-CoV-2 specific T cell responses and has been proposed as a potential biomarker for poor T-cell responses in severe COVID-19.[8]

A now well described inflammatory syndrome related to COVID-19, multisystem inflammatory syndrome in children (MIS-C), may have clinical features of Kawasaki disease with some patients also meeting criteria for macrophage activation syndrome.[44-47] The syndrome is now also well described in adults.[48] These cases are often diagnosed weeks after SARS-CoV-2 infection and treatment includes IVIG and other immunomodulating agents like steroids or anakinra. There is some overlap between the immune changes associated with this syndrome and those seen in severe COVID-19, including lymphopenia, elevation of various cytokines, and impaired antigen presentation.[49]

Clinical Data for Immunomodulation for COVID-19

Corticosteroids are widely used immunomodulatory agents for a variety of conditions. There was initial hesitation in using them for COVID-19 given an association with prolonged viral shedding when used for other SARS or MERS in non-randomized settings.[50] Steroid use in non-COVID-19-related ARDS has mixed results, with some studies suggesting a possible mortality benefit; however, steroid use for influenza pneumonia is associated with increased mortality.[51, 52] We identified 531 references on "steroids," "dexamethasone," or "methylprednisolone" and included 14 studies (Table 1). While studies have reported mixed efficacy for steroids for COVID-19, they have become standard of care for people with severe or critical COVID-19 based on the RECOVERY trial. Importantly, there is a dearth of data regarding infectious complications of corticosteroids for COVID-19. Additionally, multiple retrospective studies suggest steroid use in mild COVID-19 may be associated with prolonged viral RNA shedding.[53-56]

The RECOVERY trial showed a significant mortality benefit for dexamethasone in COVID-19, with the biggest effect in the subgroup receiving mechanical ventilation where risk of death was

decreased by a third (29.3% versus 41.4%, with a relative risk of death of 0.64, 95%CI 0.51-0.81).[22] The mortality benefit was more modest for individuals receiving supplemental oxygen but not requiring mechanical ventilation, 23.3% vs. 26.2%, rate ratio 0.82, 95%CI 0.72-0.94. Importantly among those not receiving supplemental oxygen there was no benefit seen and, indeed, a trend towards harm, 17.8% vs. 14.0%, rate ratio 1.19, 95%CI 0.91-1.55. The mean time from symptom onset for those not on supplemental oxygen was 6 days compared with 8 days for those with supplemental oxygen and 13 days for those requiring mechanical ventilation. In fact, when considering the subgroup started on steroids before 7 days of symptoms, there was no mortality benefit seen. The heterogeneity seen in the results of this trial suggests that a one-size-fits-all approach is not appropriate for treatment of COVID-19. Based on data from RECOVERY, there is strong evidence for steroid administration, preferably dexamethasone, for individuals with COVID-19 requiring supplemental oxygen or mechanical ventilation, particularly if they are beyond 7-days of symptom onset. Steroids should be avoided for individuals not requiring supplemental oxygen.

[Table 1]

Besides steroids, numerous other immunomodulatory agents have been used for COVID-19. An early report from China used IL-6 receptor blocker (tocilizumab) for the treatment of 21 patients with severe or critical disease and reported rapid and profound improvement in oxygenation, inflammatory markers, and clinical status, generating tremendous interest.[69] Our systematic evaluation identified 412 tocilizumab and 14 sarilumab peer reviewed articles related to COVID-19, of which, 13 were included here (Table 2). A preprint and two press releases of major RCTs were also included. The results from the non-randomized studies are mixed. Importantly peer reviewed results from one double blind RCT and two open-label RCTs are now available, and additional RCT results are available by preprint and press release. The results from the RCTs are largely concordant, with neither benefit nor an increased risk of secondary infections. One trial reports a benefit because a composite primary endpoint was met, but mortality at 28-days was numerically higher in the tocilizumab arm.[70] These accumulating negative

suggest that COVID-19 is not a true cytokine, specifically IL-6 mediated, storm but rather the result of more complex immune dysregulation. Additional peer-reviewed data are forthcoming, but at this time there is no evidence to support the use of IL-6 receptor inhibition for treatment of COVID-19.

[Table 2]

Use of other immunomodulatory agents is described in fewer publications. These agents include anakinra (3 studies), baricitinib (2 studies), and ruxolitinib (1 study) (Table 3). Treatment of COVID-19 with interleukin-1 receptor antagonism with anakinra has been studied, with no RCTs published to date. Two small non-randomized series have suggested a mortality benefit with this agent, but there are currently no data to support using this agent outside of a clinical trial.[85, 86]

Baricitinib and ruxolitinib are Janus kinase (JAK) inhibitors. Severe COVID-19 is associated with an imbalanced JAK and signal transducer and activator of transcription protein (STAT) pathway, with increased relative activity of STAT3 compared to STAT1, contributing to an ineffective antiviral response and a proinflammatory phenotype. Inhibition of JAK-dependent signaling can attenuate overactive STAT3 activity and theoretically ameliorate the immune dysregulation in severe COVID-19.[37, 87] Baricitinib administration is associated with normalization in cytokine profile and restoration of levels of circulating lymphocytes in patients within a small cohort of hospitalized patients with COVID-19 with fewer than 9 days of symptoms.[87] The results of the ACTT-2 trial were released by a press release, reporting faster time to clinical recovery when baricitinib was added to remdesivir. There are less robust data at this time for ruxolitinib. Based on the press release it is likely that baricitinib will have a role in the treatment of patients with COVID-19, but more details are required from peer reviewed data. Other kinase inhibitors showing preliminary good effect in the reduction of inflammatory parameters and improved oxygenation are selective blockers of Bruton's tyrosine kinase (Btk) such as acalabrutinib.[88, 89]

[Table 3]

Interferon therapy is another immunomodulatory approach being studied for treatment of COVID-19. SARS-CoV-2 is sensitive to type I interferons *in vitro* with markedly decreased viral replication.[95] SARS-CoV-2 evades the interferon response and insufficient interferon stimulation is seen in patients with severe COVID-19.[96] Taken together, this observation has led to the hypothesis that early type I interferon administration might help limit viral replication. The MIRACLE trial for MERS, which is the first RCT published for treatment of either SARS or MERS, found that interferon beta1b was associated with lower mortality in a prespecified subgroup when it was given within 7 days of symptom onset but had no effect later in the illness course.[97] It is important to note that viral load dynamics are different between MERS-CoV and SARS-CoV-2, with upper respiratory tract viral load peaking around 7-10 days for MERS-CoV and earlier for SARS-CoV-2 infection.[98] Given the earlier viral phase for SARS-CoV-2, and the fact that most people present 4-7 days after symptom onset when viral loads are already declining, it remains to be seen whether interferons have a role in the treatment of COVID-19.[99, 100]

Of 418 papers related to SARS-CoV-2 and interferons, 8 are included here (Table 4). An open label RCT evaluated treatment with triple therapy (interferon β-1b, ribavirin, and lopinavir/ritonavir) against lopinavir/ritonavir monotherapy and found that the interferon treated group had faster viral clearance from nasopharyngeal swabs of 7 days versus 12 days (p=0.001).[101] This striking result is notable since no other randomized treatment study has demonstrated such impact, including a remdesivir study,[15] and suggests that specific immune augmentation may have potent anti-SARS-CoV-2 viral effect. Preliminary data from the large WHO-sponsored SOLIDARITY trial suggest interferon beta1b administration was not associated with a change in mortality, but there is no information about the timing of administration.[19] Currently there are insufficient data to support interferon use for COVID-19 outside of a clinical trial, but further study, particularly early in disease, is needed. Given the finding of auto-antibodies to some type I interferons (most commonly interferon alpha) in severe COVID-19, interferon-beta formulations may be more likely to have effect than interferon-alpha.[40]

[Table 4]

Infectious, Noninfectious and Immunologic Unintended Consequences of Immunomodulatory Therapy

Some immunomodulatory agents are associated with an increased risk of secondary infections. Notably, tocilizumab in the setting of CAR-T-related CRS is not associated with increased infection risk compared with patients receiving similar salvage chemotherapies without this agent.[108, 109] Few published series to date report systematically on the incidence of secondary and nosocomial infections for patients receiving immunomodulatory treatment. Notably secondary infection rates are not reported in the RECOVERY trial for dexamethasone.[22] Besides common nosocomial infections including bacteremia and pneumonia, case reports document sometimes fatal secondary infections, including from HSV reactivation, disseminated Strongyloidiasis, and invasive fungal infections.[110-113] Monitoring for reactivation of other latent infections like hepatitis B and tuberculosis is also critical.[114, 115]

Noninfectious complications including osteonecrosis related to steroids and bowel perforation after IL-6 inhibitor administration have been noted.[116, 117] A larger unknown is the possible long-term immunologic consequences of immunomodulatory therapy. Cases of SARS-CoV-2 reinfection are now being reported around the globe and may be common around 12 months after initial infection.[118-120] Given the associations of a coordinated immune response and recent common coronavirus infection with less severe COVID-19, therapies that inhibit a protective immune response may keep people at risk for future severe COVID-19, particularly if reinfection is inevitable.[7, 8] All of these issues will have to be explored further in future RCTs.

Conclusions

Severe COVID-19 is marked by a protracted course with evidence of immune dysregulation and, at times, multisystem organ dysfunction. Several proposed strategies for treatment include antiviral agents and immunomodulatory therapeutics. Since SARS-CoV-2 viral loads peak around the time of symptom onset and patients with severe immune dysregulation often present 5-7 days later, an approach that is exclusively antiviral may not be sufficient for all patients. Antivirals and stimulators of innate antiviral response (i.e. interferons) may be most likely to show benefit early in the disease course when viral loads are highest, likely within 7 days of symptoms onset and sooner if possible. While early hypotheses proposed the second phase of severe COVID-19 illness course might be similar to cytokine release syndrome, immune profiling has revealed a complex immune dysregulation with a central role for the type I interferon response. Strategies to attenuate this imbalanced response including steroids and targeted therapies are all being actively studied.

Given the marked heterogeneity of COVID-19 clinical presentations, therapeutic approaches will likely need to be tailored to individual patients and a one-size-fits all approach may not provide optimal benefit. Potential therapeutic approaches will need to identify the right therapy, dose, patient and proper timing in relation to the disease course. To define these specific treatments, data from well performed RCTs are needed that include details about timing of administration of agents in the COVID-19 illness course.

NOTES

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Table 1: Review of Major COVID-19 Series using Corticosteroids as Therapy

Agent [Ref]	Country	Study Design	Target Population (n)[a]	Endpoint Measured	Outcome and Multivariable Analysis	Infectious Complications	Conclusion or Recommendation	Strength of Evidence[b]
Dexamethasone [22]	UK	Open label RCT	Hospitalized patients (2104)	Mortality at 28-days	22.9% vs. 25.7% favoring dex, age adjusted rate ratio 0.83 (95% CI 0.75-0.93)	Not reported	Mortality benefit favoring dexamethasone, strongest effect on those receiving mechanical ventilation	A
Hydrocortisone [57]	France	RCT, double blind	Critically ill patients (76)	Death or persistent mechanical ventilation or high flow nasal cannula at day 21	42.1% vs. 50.7% favoring hydrocortisone, difference of proportions -8.6% (95% CI -24.9% to 7.7%, p=0.29)	37.3% for hydrocortisone and 41.1% for placebo (HR 0.81, 95% CI 0.49-1.35, p=0.42)	No significant difference in primary outcome; study stopped early (underpowered)	A
Methylprednisolone [58]	Brazil	RCT, double blind	Hospitalized patients with severe or critical COVID-19 (194)	Mortality at 28-days	37.1% for methylpred vs 38.2% (p=0.629)	Not reported	No difference in overall mortality	A
Dexamethasone [59]	Brazil	Open label RCT	Hospitalized patients with moderate to	Ventilator-free days during first	More ventilator free days for dex (difference 2.26;	21.9% of dex and 29.1% of usual care had	Dexamethasone was associated with more days off a	A

			severe COVID-19 (151)	28 days	95% CI, 0.2-4.38, p=.04); no difference in all-cause mortality at 28 days (56.3% versus 61.5%, HR 0.97, 95% CI, 0.72-1.31, p=.85)	secondary infections	ventilator but in this study a mortality benefit was not seen	
Methylprednisolone [60]	Iran	RCT, single blind	Hospitalized patients with SpO2 <90%, elevated CRP and elevated IL-6, though excluded if ARDS, SpO2<75%, positive procalcitonin or positive troponin (34)	Time to clinical improvement and discharge or death, whichever came first	Methylprednisolone significantly associated with reduced time to primary outcome (11.6±4.8 versus 17.6±9.8 days, p=.006); mortality rate lower for methylpred group 5.9% versus 42.9%, p<0.001	Not well defined	In a small study with a highly specific group, methylprednisolone showed a benefit	A
Methylprednisolone [61]	USA (Michigan)	Single pre-test post-test quasi-experimental study	Hospitalized patients requiring supplemental oxygen (132)	Composite of escalation to ICU or all cause in-hospital mortality	Primary composite endpoint occurred in 34.9% vs. 54.3% (p=.005) favoring early steroid group; after multivariable adjustment, early corticosteroids were independently associated with a. reduction in composite outcome at day 14 (OR 0.4, 95% CI .22-.77)	Not reported	Early steroid use was associated with improved outcomes in this non-randomized trial	B
Methylprednisolone [62]	Spain	Retrospective cohort study	Hospitalized patients (396)	In-hospital mortality	Patients treated with steroids had lower mortality than those treated with	Not reported	Steroid use associated with lower mortality in this non-	B

					standard of care (13.9% vs. 23.9%, HR 0.51, 95% CI 0.27-0.96, p=0.044)		randomized trial. The finding persisted after propensity score matching	
Corticosteroids [63]	USA (New York City)	Retrospective cohort study	Hospitalized patients. Compared those who received steroids within 48 hours of admission compared with those who never received steroids (140)	Composite of in-hospital mortality or in-hospital mechanical ventilation	Early glucocorticoids were not associated with decreased in-hospital mortality, though among subgroup with CRP >20mg/dL was associated with reduced mortality or mechanical ventilation (aOR 0.20, 95% CI 0.06-0.67)	Not reported	Steroid use was not associated with improved outcomes overall; among those with an elevated CRP, steroid use was associated with improved outcomes	B
Corticosteroids [64]	China	Retrospective cohort study	Hospitalized patients (158)	In-hospital mortality	Patients who received corticosteroids had higher mortality 45.6% vs. 11.5% p<0.0001; after propensity matching there was no difference in mortality	There were more nosocomial infections among those treated with steroids 7.0% vs. 2.9%, p=0.02	This non-randomized trial found no benefit to steroids for treatment of COVID-19	B
Corticosteroids [65]	Italy	Retrospective cohort study	Hospitalized patients with severe COVID-19 (170)	Mortality at day 30 from hospital admission	35% in corticosteroid group and 31% in non-steroid group died within 30 days of hospital admission; multivariable analysis aOR 0.59, 95% CI 0.20-1.74, p=.33	17% of overall cohort had bacterial superinfections; hazard was higher for those receiving steroids, but not statistically significant (HR	This non-randomized trial found no mortality benefit for corticosteroids for severe COVID-19	B

						1.55, 95% CI 0.95-2.55, p=0.08)		
Corticosteroids [56]	China	Retrospective cohort study	Hospitalized patients (126)	Hospital length of stay	After matching, among non-severe group, steroid use associated with increased length of stay (19.0 vs. 11.5 days, p<.001). Among severe group no significant difference in length of stay (14.0 vs. 16.0 days, p=.883)	Unable to report infection rates, but antibiotic use higher among those receiving steroids (p<.001)	This non-randomized trial found no benefit to steroid use for COVID-19 and found longer hospital stay for non-severe patients who received steroids compared with matched non-steroid recipients	B
Corticosteroids [66]	USA (New York City)	Retrospective cohort study	Hospitalized patients with severe COVID-19 (SpO2/fiO2 <440) (60)	Composite outcome of ICU transfer, intubate or death	In adjusted analysis those who received steroids were less likely to have had a primary outcome, aHR 0.15, 95%CI 0.07-0.33, p<0.001	Not reported	In this non-randomized study of patients with severe COVID-19, steroid administration was associated with improved outcomes	B
Corticosteroids [67]	China	Retrospective cohort study	Hospitalized patients with severe (requiring supplemental oxygen) or critical (shock, mechanical ventilation or ICU level care) COVID-19 (531)	In-hospital mortality	In multivariable analysis steroid use was independently associated with in-hospital mortality, HR 1.77, 95% CI 1.08-2.89, p=.023	Not reported	In this non-randomized study of severe and critically ill patients with COVID-19, steroid use was associated with an increased risk of death	B
Methylprednisolone [68]	China	Retrospective cohort study	Hospitalized patients with severe or	Progression from severe to critical	In multivariate analysis, methylprednisolone	Not reported	In this non-randomized study, steroid use was	B

			critical COVID-19 (140)	illness	was associated with less risk of progression to critical illness, OR 0.054 95% CI: 0.017-0.173, p<.001. In a subgroup analysis the finding held for individuals <65 but not for those over 65 years old		associated with less progression to critical illness	

Table 1 Legend:

[a] n = number of patients in study who received immunomodulatory therapy

[b] Strength of evidence graded as: A = from a randomized control trial, B = from a non-randomized study

RCT = randomized controlled trial. 95% CI = 95% confidence interval range, HR = hazard ratio, SpO2 = peripheral capillary oxygen saturation, CRP = C-reactive protein, IL-6 = interleukin 6, ARDS = acute respiratory distress syndrome, ICU = intensive care unit, OR = odds ratio, aOR = adjusted odds ratio, fiO2 = fraction of inspired oxygen

Table 2: Major Studies Reporting IL-6 Receptor Inhibition with Tocilizumab (TCZ) or Sarilumab for COVID-19									
[Ref]	**Country**	**Co-Medications**	**Study Design**	**Target Population (n)[a]**	**Endpoint Measured**	**Outcome and Multivariable Analysis**	**Infectious Complications**	**Conclusion or Recommendation**	**Strength of Evidence[b]**
[1]	USA (Boston)	Steroids (10%), RDV (~33%), HCQ (4%)	RCT, double blind	Hospitalized patients with two of: fever, pulmonary infiltrates and need for supplemental O2 and one of: elevated CRP, D-dimer, ferritin, or LDH (161)	Intubation and mortality at day 28	10.6% in TCZ group vs. 12.5% in placebo group had been intubated or died by day 28, HR 0.83, 95%CI 0.38-1.81, p=0.64	There were fewer infectious complications in the TCZ group, 8.1% vs. 17.1%, p=0.03	This double blind RCT does not support using TCZ for patients with severe COVID-19	A
[71]	France	Azithro (~20%), HCQ (~8%), steroids (~30%, more in usual care arm)	RCT, open label	Hospitalized patients with moderate, severe or critical COVID-19 (63)	Need for ventilation and mortality	Suggestion of benefit for TCZ at day 14; however, mortality at day 28 11.1% for TCZ vs. 11.9% for stand of care, aHR 0.92, 95%CI 0.33-2.53	Secondary infections reported in 3.7% for TCZ vs. 20.9% of standard of care group	This open label RCT found no mortality benefit for TCZ at 28-days	A
[72]	Italy	Azithro (~20%), DRV/c or LPV/r (~40%)	RCT, open label	Hospitalized patients with PaO2/fiO2 of 200-300 and fever or elevated CRP (60)	Admission to ICU or death by day 14	28.3% for TCZ vs. 27.0% met primary outcome. Mortality at 30 days was 3.3% for TCZ vs. 1.6%	Secondary infections reported in 1.7% of TCZ vs. 6.3%	This open label RCT found no benefit to TCZ	A
[70]	Multi-	Steroids and	RCT, double	Hospitalized	Composite	Composite	Serious	This double blind	A (report

	national	various antivirals used in 80%	blind	patients with SpO2 ≤94% on ambient air (249)	of ventilation or mortality by day 28	outcome occurred in 12.0% for TCZ vs. 19.3%, HR 0.56, 95%CI 0.33-0.97, p=0.036; mortality at day 28 was numerically higher in the TCZ arm, 10.4% vs. 8.6%, weighted difference 2%, 95%Ci -5.2%-7.8%	infections reported in 5.2% in TCZ and 7.1% placebo	RCT met its primary composite endpoint; however, there was numerically higher mortality at 28-days in the TCZ arm	not peer reviewed)
[73]	USA and Europe	No details to date	RCT, double blind	Hospitalized patients with severe COVID-19 (~225)	Improved clinical status at day 28 and mortality	No difference in clinical status at day 28, OR 1.19, 95%CI 0.81-1.76, p=0.36; mortality 19.7% vs 19.4% with a difference of 0.3%, 95%CI -7.6%-8.2%, p=.94	No difference in secondary infections between the groups 38.3% vs. 40.6%	This double blind RCT found no benefit for TCZ for severe COVID-19	A (though data not peer reviewed)
[74]	USA (multiple sites)	No details to date	RCT, double blind	Hospitalized patients with severe-COVID-19 (~1200)	Improved clinical status and mortality	Per press report: "did not meet its primary and key secondary endpoints"	Not reported to date	This double blind RCT found no benefit for sarilumab	A (though data not peer reviewed)
[75]	Italy	HCQ and LPV/r	Retrospective cohort study	Hospitalized patients with RR ≥30, SpO2 ≤93% on ambient air, or PaO2/FiO2	Survival rate	3.2% vs 47.8% mortality favoring TCZ; aHR 0.035, 95%CI 0.004-0.347, p=0.004	No secondary infections reported in either group	This non-randomized study in patients with severe COVID-19 found TCZ was associated with decreased	B

				≤300. Critical patients excluded (62)				mortality	
[76]	Italy	HCQ + LPV/r or RDV	Retrospective cohort study	Hospitalized patients with bilateral pulmonary infiltrates and CRP >1mg/dL, IL-6 >40pg/mL, D-dimer >1.5 mcg/mL, or ferritin >500ng/mL with severe or critical COVID-19 (74)	Survival rate	TCZ use associated with improved survival, HR 0.499, 95%CI 0.262-0.952, p=0.035. Benefit highest in critical illness, no severe disease	32.4% of TCZ patients had secondary infections, but no comparison reported for standard of care group	This non-randomized study found TCZ was associated with decreased mortality. Many secondary infections were reported but no comparison was available with the standard of care group	B
[77]	USA (Michigan)	25% received steroids, 23% HCQ, 3% RDV	Retrospective cohort study	Intubated patients (78)	Survival probability after intubation	Mortality at day 28 lower for TCZ treated patients at 18% vs. 36%, p=0.01; aHR 0.54, 95%CI 0.35-0.84	TCZ treated patients more likely to have superinfection, 54% vs. 26%, p<0.001	This non-randomized study found TCZ use was associated with decreased mortality but increased rate of superinfections in a critically ill cohort	B
[78]	USA (NYC)	HCQ + azithromycin in >90%, steroids ~40%, RDV ~10%	Retrospective case-control study	Hospitalized patients with severe or critical COVID-19 (96)	Overall mortality rate	Mortality rates 52% vs. 62%, p=0.09. Excluding intubated patients 6% vs. 27%, p=0.024, favoring TCZ	Bacteremia more common in control group (23.7% vs 12.5%, p=0.04), fungemia similar 3% vs 4%, p=0.7	This non-randomized study found TCZ was associated with a lower mortality rate among non-intubated patients with COVID-19	B
[79]	Spain	HCQ (98%), LPV/r (82%), azithromycin (74%), IFN-	Retrospective cohort study	Hospitalized patients with fever or need for supplemental	Intubation or death	11.4% vs. 20.1% of patients requiring intubation or died, favoring	Rates of secondary bacterial infections were similar 12.5% vs	This non-randomized study found TCZ was associated with lower rates of	B

		B (28%), steroids (19%)		oxygen and elevated CRP, D-dimer, or ferritin (88)		TCZ. Hazard ratio after matching cases was 0.22, 95%Ci 0.05-0.96, p=0.04	10.3%, p=0.57	intubation or death with similar rates of secondary bacterial infections	
[80]	Italy	HCQ + LPV/r	Retrospective cohort study	Hospitalized patients with bilateral pulmonary opacities and either RR ≥30, SpO2 ≤93% on ambient air, or PaO2/fiO2 ≤300 (90)	Survival rate	7.7% vs. 50% mortality favoring TCZ, aHR for death 0.057, 95%CI = 0.017-0.187, p<0.001	No secondary infections observed	This non-randomized study found TCZ was associated with lower mortality in patients with COVID-19	B
[81]	USA (New Jersey)	Steroids (66%), HCQ + azithromycin (>90%)	Retrospective cohort study	Hospitalized patients with COVID-19 in the ICU (134)	Survival rate	46% vs. 56% mortality favoring TCZ, aHR 0.76, 95%CI 0.57-1.00)	13% vs 11% bacteremia	This non-randomized study found a trend towards improved mortality when TCZ was given for critical COVID-19	B
[82]	USA (Chicago)	RDV in around a third. TCZ patients more likely to get HCQ than controls (57% vs. 20%, p=0.001)	Retrospective cohort study	Hospitalized patients with severe COVID-19 with progressive hypoxemia with elevated D-dimer >2mg/L, CRP >100mg/dL, or ferritin >600mcg/L	Secondary infections and mortality	Mortality was higher among those who received TCZ 39% vs. 23%, p=0.03	Late onset infections were more commonly seen in the TC group (23% vs 8%, p=0.013)	This non-randomized trial found TCZ was associated with increased mortality and increased late onset infections	B
[83]	Italy	LPV/r (or DRV/c) and HCQ	Retrospective case-control study	Hospitalized patients with worsening oxygen	Mortality rates	Mortality was not associated with TCZ treatment, aHR	The rate of secondary infections was not different	This non-randomized trial found no mortality benefit for TCZ,	B

				requirement, elevated CRP and another in a list of abnormal labs (64)		0.82, 95%CI 0.42-1.58, p=0.55	between the groups, 31% for TCZ vs. 39%, HR 0.71, 95%CI 0.38-1.32, p-0.28	with a similar amount of secondary infectious complications	
[84]	India	HCQ, ivermectin, oseltamivir, methylpred	Retrospective cohort study	Hospitalized patients with SpO2 ≤94% despite supplemental oxygen or PaO2/fiO2 ≤200	Death	TCZ independently associated with reduced death, aHR 0.62, 95%CI 0.38-0.99	Not reported	This non-randomized trial found improved mortality among those who received TCZ	B

Table 2 Legend:

[a] n = number of patients in study who received immunomodulatory therapy

[b] Strength of evidence graded as: A = from a randomized control trial, B = from a non-randomized study

RCT = randomized controlled trial. 95% CI = 95% confidence interval range, HR = hazard ratio, aHR = adjusted hazard ratio, SpO2 = peripheral capillary oxygen saturation, CRP = C-reactive protein, IL-6 = interleukin 6, ARDS = acute respiratory distress syndrome, ICU = intensive care unit, OR = odds ratio, aOR = adjusted odds ratio, fiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen, RR = respiratory rate, TCZ = tocilizumab, HCQ = hydroxychloroquine, LPV/r = lopinavir with ritonavir, RDV = remdesivir, IFN-β = interferon beta, DRV/c = darunavir with cobicistat

Table 3: Summary of Additional Immunomodulatory COVID-19 Series								
Agent [Ref]	**Country**	**Study Design**	**Target Population (n)[a]**	**Endpoint Measured**	**Outcome and Multivariable Analysis**	**Infectious Complications**	**Conclusion or Recommendation**	**Strength of Evidence[b]**
Anakinra [85]	Italy	Retrospective cohort study	Hospitalized patients with moderate to severe COVID-19 with hyper-inflammation, with CRP ≥100 mg/dL or ferritin ≥900 ng/mL (29)	Survival rates	Mortality was 10% in the anakinra group and 44% in the standard treatment group, p=0.009	Bacteremia in 14% anakinra vs. 13% standard treatment	In this small non-randomized study, anakinra was associated with decreased mortality among patients with severe COVID-19 and laboratory evidence of inflammation	B
Anakinra [86]	France	Retrospective cohort study	Hospitalized patients with severe COVID-19 (52)	Composite of ICU admission, need for mechanical ventilation or death	Composite less common in those who received anakinra compared with historical controls (25% vs. 73%, HR 0.22, 95%CI 0.11-0.41, p<0.0001)	No secondary bacterial infections documented	In this non-randomized study, anakinra was associated with reduced mortality compared with a historical control	B
Anakinra [90]	USA (LA)	Retrospective cohort study	Hospitalized patients with COVID-19 with progressive hypoxemia and bilateral pulmonary infiltrates (52)	Survival rates	Mortality was lower in anakinra group (22%) than TCZ group (46.2%); after adjustment, aHR 0.46, 95%CI 0.18-1.20, p=0.11)	Not reported	In this non-randomized study that compared anakinra to TCZ administration, there was no statistically significant difference in mortality between the two agents	B
Baricitinib [91]	Global (NIH)	RCT, double blind	Hospitalized patients with COVID-19 (~500)	Time to clinical recovery	Study met primary endpoint	Not reported	In this double-blind randomized control trial, baricitinib improved time to clinical recovery when added to remdesivir	A
Baricitinib [92]	Italy	Retrospective cohort study	Hospitalized patients with	Mortality rate at 2	Lower mortality in baricitinib arm 0% vs	Not reported	In this non-randomized study, baricitinib was	B

			moderate COVID-19 with radiographic pneumonia, SpO2 >92% on room air and PaO2/fiO2 100-300 (113)	weeks	6.4%, p=0.010		associated with improved mortality at 2 weeks compared with historical controls; PCR positivity was significantly lower at day 14 for those who received baricitinib, 12.5 vs. 40%	
Baricitinib [93]	Spain	Prospective cohort study	Hospitalized patients with severe COVID-19 with PaO2/fiO2 <200 (62)	Improved SpO2/fiO2	A greater improvement in SpO2/fiO2 was seen for those who received baricitinib	Two bacteremias in control group, none in baricitinib group	In this non-randomized study, baricitinib improved oxygenation when added to steroids and multiple other "standard therapies" compared with those therapies alone	B
Ruxolitinib [94]	China	RCT, single blind	Hospitalized patients with severe COVID-19 (20)	Time to improved clinical status, mortality	Patients who received ruxolitinib had a numerically shorter time to clinical improvement, 12 vs 15 days, HR 1.67, 95%CI 0.84-3.34, p=0.15; mortality at day 28 was 0% for ruxolitinib vs. 14.3%, but cumulative incidence of death was the same between the groups	Two secondary infections in control group and none in ruxolitinib group	This small RCT found numerically faster but not statistically significant clinical improvement for those who received ruxolitinib	A

Table 3 Legend:

[a] n = number of patients in study who received immunomodulatory therapy

[b] Strength of evidence graded as: A = from a randomized control trial, B = from a non-randomized study

RCT = randomized controlled trial. 95% CI = 95% confidence interval range, HR = hazard ratio, aHR = adjusted hazard ratio, SpO2 = peripheral capillary oxygen saturation, CRP = C-reactive protein, ICU = intensive care unit, OR = odds ratio, aOR = adjusted odds ratio, fiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen, RR = respiratory rate, TCZ = tocilizumab, PCR = polymerase chain reaction

Table 4: Series Reporting Data for Interferon for Treatment of COVID-19

Type of IFN [Ref]	Country	Co-Medications	Study Design	Target Population (n)[a]	Endpoint Measured	Outcome and Multivariable Analysis	Infectious Complications	Conclusion or Recommendation	Strength of Evidence[b]
IFN beta [102]	Hong Kong	LPV/r + ribavirin, 7% steroids	RCT, open label	Hospitalized patients with COVID-19 and NEWS2 ≥1, with symptoms ≤14 days (86)	Time to negative PCR, mortality	Combination therapy associated with significantly shorter median time to PCR negativity, 7 vs. 12 days, HR 4.37, 95%CI 1.86-10.24, p=0.001, no patients died in either arm	Not reported	In this RCT, where treatments were started around day 5 after symptom onset in a relatively mild cohort, combination therapy with IFN-beta1b, ribavirin, and LPV/r showed faster viral clearance compared with LPV/r only	A
IFN beta [103]	Iran	HCQ + LPV/r or ATV/r, 62% received	RCT, open label	Hospitalized patients with severe COVID-19	Time to clinical improvement	No difference in time to clinical	There were numerically more	In this RCT, IFN-beta1a did not increase time to	A

		steroids		with either hypoxemia, hypotension, renal failure, neurologic change, thrombocytopenia, or severe GI symptoms		improvement between the groups 9.7 days for IFN vs 8.3 days, p=0.95, HR 1.10, 95%CI 0.64-1.87; however day 28 mortality lower in IFN group 19% vs. 43.6%, p=0.015, when adjusted for IVIG and steroid administration effect remained, aHR 0.375, 95%CI 0.16-0.87, p=0.024	nosocomial infections in the IFN group, 26.2% vs. 12.8%, p=0.09	clinical improvement but was associated with lower mortality even after controlling for steroid use. IFN was started a mean of 11.7 days after symptom onset	
IFN beta [104]	Iran	LPV/r or ATV/r + HCQ, steroids in nearly 30%	RCT, open label	Hospitalized patients with severe COVID-19 (33)	Time to improved clinical status	Time to clinical improvement was shorter for the IFN group, 9 vs. 11 days, p=0.002; aHR=3.41, 95%CI 1.33-8.72	Nosocomial infections in 3% vs18% favoring IFN	In this small RCT, IFN-beta1b was associated with reduced mortality among a cohort with severe COVID-19. Started at mean 7 days of symptom onset	A
IFN beta [19]	Multi-national (WHO)	LPV/r or "local standard of care"	RCT, open label	Hospitalized patients with COVID-19 (2050)	Mortality	12.9% deaths for IFN vs. 11.0% for controls, no difference	Not reported	In this open label RCT, IFN-beta1a was not associated with improved outcomes. There is no data yet available about when in the illness course the	A

								treatment was given	
IFN alpha [105]	China	Arbidol	Retrospective cohort study	Hospitalized patients with moderate COVID-19 (53)	Time to negative upper respiratory tract PCR test	IFN was associated with accelerated viral clearance from the upper respiratory tract by ~7 days, p=0.002	Not reported	In this non-randomized study, IFN-alpha2b therapy was associated with more rapid viral clearance from the upper respiratory tract	B
IFN alpha [106]	Cuba	LPV/r + CQ	Prospective cohort study	Hospitalized patients with COVID-19 (761)	Time to discharge and mortality	Mortality reported much lower in IFN group	Not reported	In this highly confounded non-randomized study where there were significant age and comorbidity differences between the groups IFN-alpha2b was associated with improved outcomes	B
IFN alpha [107]	China	Nearly 80% received LPV/r, 60% steroids, around 40% IVIG	Retrospective case-control study	Hospitalized patients with COVID-19 (68)	Time to negative upper respiratory tract PCR	Time to negative PCR was not shorter for IFN after propensity matching, 12 vs. 15 days, p=0.206.	Not reported	In this non-randomized study, IFN-alpha2b did not have an effect on time to negative upper respiratory tract PCR	B
IFN alpha [96]	China	LPV/r or arbidol	Retrospective cohort study	(216)	Mortality	Early IFN therapy was associated with lower mortality, aHR 0.10, 95%CI 0.02-0.50. Among the 26 who received	Not reported	In this non-randomized study, early IFN-alpha2b (defined as given within 48 hours of admission) was associated with reduced mortality	B

						late IFN, there was increased mortality, aHR 2.30, 95%CI 0.64-8.27 compared with no IFN therapy.			

Table 4 Legend:

[a] n = number of patients in study who received immunomodulatory therapy

[b] Strength of evidence graded as: A = from a randomized control trial, B = from a non-randomized study

RCT = randomized controlled trial. 95% CI = 95% confidence interval range, HR = hazard ratio, aHR = adjusted hazard ratio, SpO2 = peripheral capillary oxygen saturation, CRP = C-reactive protein, IL-6 = interleukin 6, ARDS = acute respiratory distress syndrome, ICU = intensive care unit, OR = odds ratio, aOR = adjusted odds ratio, fiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen, RR = respiratory rate, TCZ = tocilizumab, HCQ = hydroxychloroquine, CQ = chloroquine, LPV/r = lopinavir with ritonavir, RDV = remdesivir, IFN-β = interferon beta, DRV/c = darunavir with cobicistat, ATV/r = atazanavir with ritonavir, NEWS2 = National Early Warning Score 2, PCR = polymerase chain reaction, IVIG = intravenous immunoglobulin

Figure Legends

Figure 1: *Panel A.* Schematic of the mild illness course for COVID-19 with an effective early innate response and an early, coordinated adaptive immune response. *Panel B.* Schematic of the severe illness course for COVID-19 where an ineffective innate immune response including an attenuated type I interferon response and poor antigen presentation as well as a late an uncoordinated adaptive immune response are associated with poor viral control (higher upper respiratory tract viral load) and proinflammatory, immune dysregulated profile. CXCL10 has been proposed as a possible biomarker for an ineffective specific T cell response to SARS-CoV-2.

Figure 1: Comparing Mild and Severe COVID-19 Illness Course