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REVIEW ARTICLE

Immunomodulation as Treatment for Severe Coronavirus Disease 2019: A Systematic Review of Current Modalities and Future Directions

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In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, viral load peaks early and declines quickly after symptom onset. Severe coronavirus disease 2019 (COVID-19) is marked by aberrant innate and adaptive immune responses with an abnormal cytokine profile and multiorgan system dysfunction that persists well after viral clearance. A purely antiviral treatment strategy may therefore be insufficient, and antiviral agents have not shown a benefit later in the illness course. A number of immunomodulatory strategies are being tested, including corticosteroids, cytokine and anticytokine therapies, small molecule inhibitors, and cellular therapeutics. To date, the only drug to show a mortality benefit for COVID-19 in a randomized, controlled trial is dexamethasone. However, there remains uncertainty about which patients may benefit most and about longer-term complications, including secondary infections. Here, we review the immune dysregulation of severe COVID-19 and the existing data behind various immunomodulatory strategies, and we consider future directions of study.

Keywords. COVID-19; SARS-CoV-2; immunomodulation; hyperinflammatory; cytokine storm.

Infection with severe acute respiratory 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 that require supplemental oxygen, including up to 5% who may develop critical illness [1]. Infection fatality rates are population- and age-dependent, with very low rates for children and young adults, but mortality rates >25% for individuals aged >90 years [2]. 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 [3, 4]. 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 naive T cells to respond to new viral antigens in older adults [5–7]. Autopsy studies demonstrate that the primary pulmonary pathology is diffuse alveolar damage, with micro- and macrovascular thrombosis [8].

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 [9–11]. 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 [12, 13]. 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 nonrandomized 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 showed efficacy when given early to rhesus macaques as well as improvement in time to recovery in the large RCT Adaptive COVID-19 Treatment Trial (ACTT)-1, which compared remdesivir with placebo [14–16]. There was a suggestion of a mortality benefit in patients on supplemental oxygen but not in the intensive care unit (ICU),

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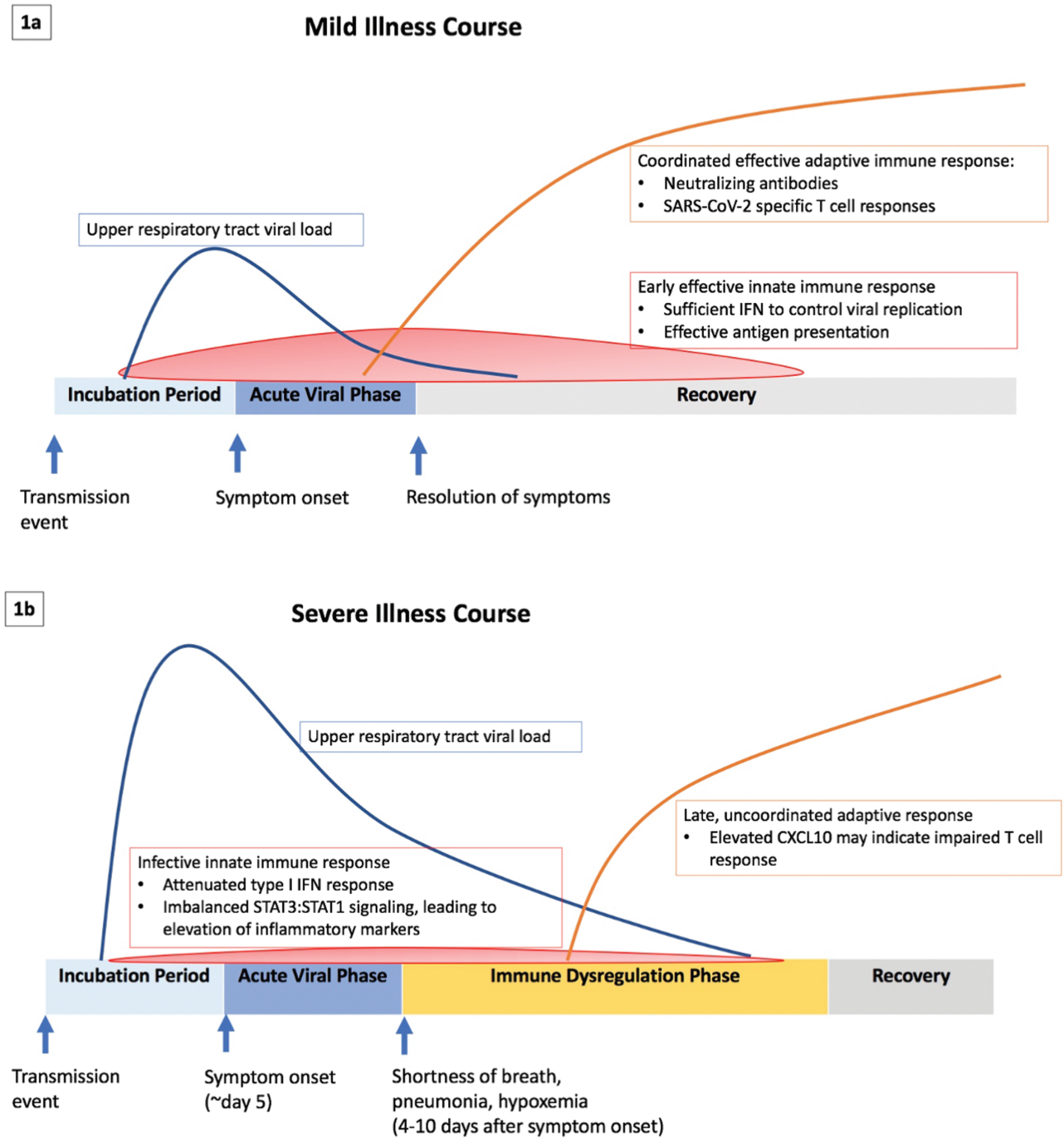

Figure 1. *A,* Schematic of the mild illness course for coronavirus disease 2019 (COVID-19) with an effective early innate response and an early, coordinated adaptive immune response. *B,* Schematic of the severe illness course for COVID-19 where an ineffective innate immune response including an attenuated type I interferon response and poor antigen presentation as well as a late uncoordinated adaptive immune response are associated with poor viral control (higher upper respiratory tract viral load) and proinflammatory, immune dysregulated profile. C-X-C motif chemokine ligand 10 (CXCL10) has been proposed as a possible biomarker for an ineffective specific T-cell response to SARS-CoV-2. Abbreviations: CXCL10, C-X-C motif chemokine ligand 10; IFN, interferon; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STAT, signal transducer and activator of transcription protein.

with no or minimal survival benefit seen for those with critical disease [16–18]. A challenge to antiviral therapy for COVID-19 is that patients with severe disease tend to present after 5–7 days of symptoms when viral loads are declining [19, 20].

The only agent yet to show a mortality benefit for COVID-19 is dexamethasone. In a large, open-label, UK-based RCT called Randomized Evaluation of Covid-19 Therapy (RECOVERY), more than 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%, $P < .001$). 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 [21]. 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 phase 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 tumor necrosis factor (TNF)-α inhibitors compared with similar cohorts on chronic steroids [22, 23].

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 1 January 2020 through 21 October 2020 using the following terms: corticosteroids, methylprednisolone, dexamethasone, tocilizumab, sarilumab, ruxolitinib, baricitinib, anakinra, and interferons. All RCTs were included, regardless of study size. Nonrandomized 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 studies were included.

ACCUMULATING EVIDENCE FOR AN IMMUNE DYSREGULATION THAT CONTRIBUTE TO SEVERE COVID-19

Early reports of patients with severe COVID-19 describe marked derangements in inflammatory markers, including elevated levels of interleukin-6 (IL-6), ferritin, and C-reactive protein, each associated with severe outcomes [24, 25]. For example, high IL-6 levels are associated with progression to mechanical ventilation [26], elevated SARS-CoV-2 viremia, and longer viral RNA shedding [27–29]. Detailed cytokine profiling has noted significant differences between survivors and nonsurvivors in other markers of inflammation, including IL-2 receptor, IL-8, IL-10, and TNF-α [30]. 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 that circulates at abnormally high levels may result in a signaling cascade, leading to vascular permeability and multisystem organ dysfunction [31]. In CRS, targeting the IL-6 axis was lifesaving [32] 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 cytokines are elevated in severe COVID-19, they are less elevated than for other conditions, including bacterial and non–COVID-19 acute respiratory distress syndrome (ARDS) [33, 34]. 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 chemokine ligand 2 (CCL2) and chemokine ligand 8 (CCL8) (which recruit macrophages) and CXCL2 and CXCL8 (which recruit neutrophils) [35]. 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 [35]. This cytokine milieu recruits and activates neutrophils, macrophages, and T lymphocytes [36]. In another study of critically ill patients with COVID-19, circulating CD8+ T lymphocytes showed significant reductions in cytokines, and natural killer cells had decreased intracellular expression of antiviral cytotoxic mediators granzyme A and perforin, consistent with an "exhausted phenotype" [37].

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 autoantibodies against type I interferons are present (and overrepresented) in some patients with severe COVID-19 [38, 39]. Additionally, the SARS-CoV-2 genome encodes structural and nonstructural proteins that antagonize type I interferons [40]. At the same time, interferon-ß inhibits SARS-CoV-2 replication [41]. Attenuation of the type I interferon response is associated with inhibition of signal transducer and activator of transcription protein (STAT1) and activation of STAT3 signaling, which has myriad downstream effects, including induction of various inflammatory cytokines and dampening an effective T-cell response [42].

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 [7]. 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 [7].

A now well-described inflammatory syndrome related to COVID-19, multisystem inflammatory syndrome in children, may have clinical features of Kawasaki disease, with some patients also meeting criteria for macrophage activation syndrome [43–46]. The syndrome is now also well described in adults [47]. These cases are often diagnosed weeks after SARS-CoV-2 infection, and treatment includes intravenous immunoglobulin and other immunomodulating agents such as steroids and 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 [48].

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 Middle East respiratory syndrome (MERS) in nonrandomized settings [49]. Steroid use in non-COVID-19–related ARDS has had mixed results, with some studies suggesting a possible mortality benefit; however, steroid use for influenza pneumonia is associated with increased mortality [50, 51]. 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 [52–55].

The RECOVERY trial showed a significant mortality benefit for dexamethasone in COVID-19, with the biggest effect in the subgroup that received mechanical ventilation where risk of death was decreased by one-third (29.3% vs 41.4%, with a relative risk of death of 0.64; 95% confidence interval [CI], .51 to .81) [21]. The mortality benefit was more modest for individuals who received supplemental oxygen but did not require mechanical ventilation (23.3% vs 26.2%; rate ratio, 0.82; 95% CI, .72 to .94). Importantly, among those who did not receive supplemental oxygen, there was no benefit seen and, indeed, a trend toward harm (17.8% vs 14.0%; rate ratio, 1.19; 95% CI, .91 to 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 who required mechanical ventilation. In fact, when the subgroup started on steroids before 7 days of symptoms is considered, no mortality benefit was 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 the RECOVERY trial, there is strong evidence for steroid administration, preferably dexamethasone, for individuals with COVID-19 who require supplemental oxygen or mechanical ventilation, particularly if they are beyond 7 days of symptom onset. Steroids should be avoided for individuals who do not require supplemental oxygen.

In addition to steroids, numerous other immunomodulatory agents have been used for COVID-19. In an early report from China, it was noted that a IL-6 receptor blocker (tocilizumab) was used to treat 21 patients with severe or critical disease, and rapid and profound improvements in oxygenation, inflammatory markers, and clinical status were reported, generating tremendous interest [68]. Our systematic evaluation identified 412 tocilizumab and 14 sarilumab peer-reviewed articles related to COVID-19, of which 13 are included here (Table 2). A preprint and 2 press releases of major RCTs were also included. The results from the nonrandomized studies are mixed. Importantly, peer-reviewed results from 1 double-blind RCT and 2 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 reported a benefit because a composite primary endpoint was met, but mortality at 28 days was numerically higher in the tocilizumab arm [69]. These accumulating negative results 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; however, at this time, there is no evidence to support the use of IL-6 receptor inhibition for treatment of COVID-19.

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 the IL-1 receptor antagonism anakinra has been studied, with no RCTs published to date. Two small nonrandomized series have suggested a mortality benefit with this agent, but there are currently no data to support use of 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 STAT pathway, with increased relative activity of STAT3 compared with 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 [36, 92]. Baricitinib administration was associated with normalization in the cytokine profile and restoration of circulating lymphocytes levels within a small cohort of hospitalized patients with COVID-19 with fewer than 9 days of symptoms [92]. The results of the ACTT-2 trial were released via a press release, reporting faster time to clinical recovery when baricitinib was added to remdesivir. There are fewer 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 that are showing preliminary good effect in the reduction of inflammatory parameters and improved oxygenation are selective blockers of Bruton's tyrosine kinase such as acalabrutinib [93, 94].

Interferon therapy is another immunomodulatory approach being studied for treatment of COVID-19. SARS-CoV-2 is

Table 1. Review of Major Coronavirus Disease 2019 Series That Used 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 [21]	United Kingdom	Open-label, RCT	Hospitalized patients (2104)	Mortality at 28 days	22.9% vs 25.7% favoring dexamethasone, age-adjusted rate ratio 0.83 (95% CI, .75 to .93)	Not reported	Mortality benefit favoring dexamethasone, strongest effect on those receiving mechanical ventilation	A
Hydrocortisone [56]	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%; $P = .29$)	37.3% for hydrocortisone and 41.1% for placebo (HR, 0.81; 95% CI, .49 to 1.35; $P = .42$)	No significant difference in primary outcome; study stopped early (underpowered)	A
Methylprednisolone [57]	Brazil	RCT, double-blind	Hospitalized patients with severe or critical COVID-19 (194)	Mortality at 28 days	37.1% for methylprednisolone vs 38.2% ($P = .629$)	Not reported	No difference in overall mortality	A
Dexamethasone [58]	Brazil	Open-label, RCT	Hospitalized patients with moderate to severe COVID-19 (151)	Ventilator-free days during first 28 days	More ventilator-free days for dexamethasone (difference 2.26; 95% CI, .2 to 4.38; $P = .04$); no difference in all-cause mortality at 28 days (56.3% vs 61.5%; HR, 0.97; 95% CI, .72 to 1.31; $P = .85$)	21.9% of dexamethasone and 29.1% of usual care had secondary infections	Dexamethasone was associated with more days off of a ventilator; however, in this study, a mortality benefit was not seen	A
Methylprednisolone [59]	Iran	RCT, single-blind	Hospitalized patients with SpO_2 <90%, elevated CRP, and elevated interleukin-6, though excluded if acute respiratory distress syndrome, SpO_2 <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 days vs 17.6 ± 9.8 days, $P = .006$); mortality rate lower for methylprednisolone group (5.9% vs 42.9%, $P < .001$)	Not well defined	In a small study with a highly specific group, methylprednisolone showed a benefit	A
Methylprednisolone [60]	United States (Michigan)	Single pre-test post-testquasiexperimental 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 to .77)	Not reported	Early steroid use was associated with improved outcomes in this nonrandomized trial	B
Methylprednisolone [61]	Spain	Retrospective cohort study	Hospitalized patients (396)	In-hospital mortality	Patients treated with steroids had lower mortality than those treated with standard of care (13.9% vs 23.9%; HR, 0.51; 95% CI, .27 to .96; $P = .044$)	Not reported	Steroid use associated with lower mortality in this nonrandomized trial; the finding persisted after propensity score matching	B
Corticosteroids [62]	United States (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 >20 mg/dL was associated with reduced mortality or mechanical ventilation (adjusted OR, 0.20; 95% CI, .06 to .67)	Not reported	Steroid use was not associated with improved outcomes overall; among those with elevated CRP, steroid use was associated with improved outcomes	B

Table 1. Continued

Agent [Ref]	Country	Study Design	Target Population (n)[a]	Endpoint Measured	Outcome and Multivariable Analysis	Infectious Complications	Conclusion or Recommendation	Strength of Evidence[b]
Corticosteroids [63]	China	Retrospective cohort study	Hospitalized patients (158)	In-hospital mortality	Patients who received corticosteroids had higher mortality (45.6% vs 11.5%, $P < .0001$); after propensity matching; there was no difference in mortality	There were more nosocomial infections among those treated with steroids (7.0% vs 2.9%, $P = .02$)	This nonrandomized trial found no benefit of steroids for treatment of COVID-19	B
Corticosteroids [64]	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 nonsteroid group died within 30 days of hospital admission; multivariable analysis adjusted OR, 0.59; 95% CI, .20 to 1.74; $P = .33$	17% of overall cohort had bacterial superinfections; hazard was higher for those who received steroids but not statistically significant (HR, 1.55; 95% CI, .95 to 2.55; $P = .08$)	This nonrandomized trial found no mortality benefit of corticosteroids for severe COVID-19	B
Corticosteroids [55]	China	Retrospective cohort study	Hospitalized patients (126)	Hospital length of stay	After matching, among nonsevere group, steroid use associated with increased length of stay (19.0 days vs 11.5 days, $P < .001$); among severe group, no significant difference in length of stay (14.0 days vs 16.0 days, $P = .883$)	Unable to report infection rates, but antibiotic use higher among those who received steroids ($P < .001$)	This nonrandomized trial found no benefit of steroid use for COVID-19 and found longer hospital stay for nonsevere patients who received steroids compared with matched nonsteroid recipients	B
Corticosteroids [65]	United States (New York City)	Retrospective cohort study	Hospitalized patients with severe COVID-19 (SpO_2/fiO_2 <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 (adjusted HR, 0.15; 95% CI, .07 to .33; $P < .001$)	Not reported	In this nonrandomized study of patients with severe COVID-19, steroid administration was associated with improved outcomes	B
Corticosteroids [66]	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 to 2.89; $P = .023$)	Not reported	In this nonrandomized study of severe and critically ill patients with COVID-19, steroid use was associated with an increased risk of death	B
Methylprednisolone [67]	China	Retrospective cohort study	Hospitalized patients with severe or critical COVID-19 (140)	Progression from severe to critical illness	In multivariate analysis, methylprednisolone was associated with less risk of progression to critical illness (OR, 0.054; 95% CI, .017 to .173; $P < .001$); in a subgroup analysis, the finding held for individuals aged <65 years but not for those aged >65 years	Not reported	In this nonrandomized study, steroid use was associated with less progression to critical illness	B

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; fiO_2, fraction of inspired oxygen; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; RCT, randomized, controlled trial; Ref, reference; SpO_2, peripheral capillary oxygen saturation.

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

[b]Strength of evidence graded as: A = from a randomized, controlled trial; B = from a nonrandomized study.

Table 2. Major Studies Reporting Interleukin-6 Receptor Inhibition With Tocilizumab or Sarilumab for Coronavirus Disease 2019

Reference	Country	Comedications	Study Design	Target Population (n)[a]	Endpoint Measured	Outcome and Multivariable Analysis	Infectious Complications	Conclusion or Recommendation	Strength of Evidence[b]
70	United States (Boston)	Steroids (10%), RDV (~33%), HCQ (4%)	RCT, double-blind	Hospitalized patients with 2 of the following: fever, pulmonary infiltrates, need for supplemental oxygen and 1 of the following: elevated CRP, D-dimer, ferritin, or lactate dehydrogenase (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, .38 to 1.81; $P = .64$)	There were fewer infectious complications in the TCZ group (8.1% vs 17.1%, $P = .03$)	This double-blind RCT does not support using TCZ for patients with severe COVID-19	A
71	France	Azithromycin (~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, .33 to 2.53)	Secondary infections reported in 3.7% for TCZ vs 20.9% for standard-of-care group	This open-label RCT found no mortality benefit for TCZ at 28 days	A
72	Italy	Azithromycin (~20%), DRV/c or LPV/r (~40%)	RCT, open-label	Hospitalized patients with PaO_2/fiO_2 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 of TCZ	A
69	Multinational	Steroids and various antivirals used in 80%	RCT, double-blind	Hospitalized patients with SpO_2 ≤94% on ambient air (249)	Composite of ventilation or mortality by day 28	Composite outcome occurred in 12.0% for TCZ vs 19.3% (HR, 0.56; 95% CI, .33 to 0.97; $P = .036$); mortality at day 28 was numerically higher in the TCZ arm (10.4% vs 8.6%, weighted difference, 2%; 95% CI, –5.2% to 7.8%	Serious infections reported in 5.2% in TCZ and 7.1% placebo	This double-blind RCT met its primary composite endpoint; however, there was numerically higher mortality at 28 days in the TCZ arm	A (report not peer reviewed)
73	United States 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 (odds ratio, 1.19; 95% CI, .81 to 1.76; $P = .36$); mortality 19.7% vs 19.4% with a difference of 0.3% (95% CI, –7.6% to 8.2%; $P = .94$)	No difference in secondary infections between the groups (38.3% vs 40.6%)	This double-blind RCT found no benefit of TCZ for severe COVID-19	A (though data not peer reviewed)
74	United States (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, SpO_2 ≤93% on ambient air, or PaO_2/fiO_2 ≤300; critical patients excluded (62)	Survival rate	3.2% vs 47.8% mortality favoring TCZ (aHR, 0.035; 95% CI, .004 to .347; $P = .004$)	No secondary infections reported in either group	This nonrandomized study in patients with severe COVID-19 found TCZ was associated with decreased mortality	B
76	Italy	HCQ + LPV/r or RDV	Retrospective cohort study	Hospitalized patients with bilateral pulmonary infiltrates and CRP >1 mg/dL, interleukin-6 >40 pg/mL, D-dimer >1.5 µg/mL, or ferritin >500 ng/mL with severe or critical COVID-19 (74)	Survival rate	TCZ use associated with improved survival (HR, 0.499; 95% CI, .262 to .952; $P = .035$); 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 nonrandomized 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

Table 2. Continued

Reference	Country	Comedications	Study Design	Target Population (n)[a]	Endpoint Measured	Outcome and Multivariable Analysis	Infectious Complications	Conclusion or Recommendation	Strength of Evidence[b]
77	United States (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% ($P = .01$; aHR, 0.54; 95% CI, .35 to .84)	TCZ-treated patients more likely to have superinfection (54% vs 26%, $P < .001$)	This nonrandomized study found TCZ use was associated with decreased mortality but increased rate of superinfections in a critically ill cohort	B
78	United States (New York City)	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% ($P = .09$); excluding intubated patients 6% vs 27% ($P = .024$), favoring TCZ	Bacteremia more common in control group (23.7% vs 12.5%, $P = .04$), fungemia similar (3% vs 4%, $P = .7$)	This nonrandomized study found TCZ was associated with a lower mortality rate among nonintubated patients with COVID-19	B
79	Spain	HCQ (98%), LPV/r (82%), azithromycin (74%), interferon-ß (28%), steroids (19%)	Retrospective cohort study	Hospitalized patients with fever or need for supplemental oxygen and elevated CRP, D-dimer, or ferritin (88)	Intubation or death	11.4% vs 20.1% of patients required intubation or died, favoring TCZ; HR after matching cases was 0.22 (95% CI, .05 to .96; $P = .04$)	Rates of secondary bacterial infections were similar (12.5% vs 10.3%, $P = .57$)	This nonrandomized study found TCZ was associated with lower rates of intubation or death with similar rates of secondary bacterial infections	B
80	Italy	HCQ + LPV/r	Retrospective cohort study	Hospitalized patients with bilateral pulmonary opacities and RR ≥30, SpO_2 ≤93% on ambient air, or PaO_2/fiO_2 ≤300 (90)	Survival rate	7.7% vs 50% mortality favoring TCZ, aHR for death was 0.057 (95% CI, .017 to .187; $P < .001$)	No secondary infections observed	This nonrandomized study found TCZ was associated with lower mortality in patients with COVID-19	B
81	United States (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, .57 to 1.00)	13% vs 11% bacteremia	This nonrandomized study found a trend toward improved mortality when TCZ was given for critical COVID-19	B
82	United States (Chicago)	RDV in around one-third; TCZ patients more likely to get HCQ than controls (57% vs 20%, $P = .001$)	Retrospective cohort study	Hospitalized patients with severe COVID-19 with progressive hypoxemia with elevated D-dimer >2 mg/L, CRP >100 mg/dL, or ferritin > 600 µg/L	Secondary infections and mortality	Mortality was higher among those who received TCZ (39% vs 23%, $P = .03$)	Late-onset infections were more commonly seen in the TCZ group (23% vs 8%, $P = .013$)	This nonrandomized 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 requirement, elevated CRP, and another in a list of abnormal laboratory results (64)	Mortality rates	Mortality was not associated with TCZ treatment (aHR, 0.82; 95% CI, .42 to 1.58; $P = .55$)	The rate of secondary infections was not different between the groups, 31% for TCZ vs 39% (HR, 0.71; 95% CI, .38 to 1.32, $P = 0.28$)	This nonrandomized trial found no mortality benefit for TCZ, with a similar amount of secondary infectious complications	B
[84]	India	HCQ, ivermectin, oseltamivir, methylprednisolone	Retrospective cohort study	Hospitalized patients with SpO_2 ≤94% despite supplemental oxygen or PaO_2/fiO_2 ≤200	Death	TCZ independently associated with reduced death (aHR, 0.62; 95% CI, .38 to .99)	Not reported	This nonrandomized trial found improved mortality among those who received TCZ	B

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DRV/c, darunavir with cobicistat; fiO_2, fraction of inspired oxygen; HCQ, hydroxychloroquine; HR, hazard ratio; ICU, intensive care unit; LPV/r, lopinavir with ritonavir; PaO_2, partial pressure of oxygen; RCT, randomized, controlled trial; RDV, remdesivir; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation; TCZ, tocilizumab.

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

[b]Strength of evidence graded as: A = from a randomized, controlled trial; B = from a nonrandomized study.

Table 3. Summary of Additional Immunomodulatory Coronavirus Disease 2019 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 hyperinflammation, with C-reactive protein ≥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 ($P = .009$)	Bacteremia in 14% anakinra vs 13% standard treatment	In this small nonrandomized 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 intensive care unit 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, .11 to .41; $P < .0001$)	No secondary bacterial infections documented	In this nonrandomized study, anakinra was associated with reduced mortality compared with a historical control	B
Anakinra [87]	United States (Los Angeles)	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 (adjusted HR, 0.46; 95% CI, .18 to 1.20; $P = .11$)	Not reported	In this nonrandomized study that compared anakinra with TCZ administration, there was no statistically significant difference in mortality between the 2 agents	B
Baricitinib [88]	Global (National Institutes of Health)	RCT, double-blind	Hospitalized patients with COVID-19 (~500)	Time to clinical recovery	Study met primary endpoint	Not reported	In this double-blind, randomized, controlled trial, baricitinib improved time to clinical recovery when added to remdesivir	A
Baricitinib [89]	Italy	Retrospective cohort study	Hospitalized patients with moderate COVID-19 with radiographic pneumonia, SpO_2 >92% on room air, and PaO_2/fiO_2 100–300 (113)	Mortality rate at 2 weeks	Lower mortality in baricitinib arm (0% vs 6.4%, $P = .010$)	Not reported	In this nonrandomized study, baricitinib was associated with improved mortality at 2 weeks compared with historical controls; polymerase chain reaction positivity was significantly lower at day 14 for those who received baricitinib (12.5% vs 40%)	B
Baricitinib [90]	Spain	Prospective cohort study	Hospitalized patients with severe COVID-19 with PaO_2/fiO_2 <200 (62)	Improved SpO_2/fiO_2	A greater improvement in SpO_2/fiO_2 was seen for those who received baricitinib	Two bacteremias in control group, none in baricitinib group	In this nonrandomized study, baricitinib improved oxygenation when added to steroids and multiple other "standard therapies" compared with those therapies alone	B
Ruxolitinib [91]	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 days vs 15 days; HR, 1.67; 95% CI, .84 to 3.34; $P = .15$); 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

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; fiO_2, fraction of inspired oxygen; HR, hazard ratio; RCT, randomized, controlled trial; Ref, reference; SpO_2, peripheral capillary oxygen saturation; TCZ, tocilizumab.

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

[b] Strength of evidence graded as: A = from a randomized, controlled trial, B = from a nonrandomized study.

Table 4. Series Reporting Data for Interferon for Treatment of Coronavirus Disease 2019

Type of IFN [Ref]	Country	Comedications	Study Design	Target Population (n)[a]	Endpoint Measured	Outcome and Multivariable Analysis	Infectious Complications	Conclusion or Recommendation	Strength of Evidence[b]
IFN-β [101]	Hong Kong	LPV/r + ribavirin, 7% steroids	RCT, open-label	Hospitalized patients with COVID-19 and National Early Warning Score 2, ≥1, with symptoms ≤14 days (86)	Time to negative PCR, mortality	Combination therapy associated with significantly shorter median time to PCR negativity (7 days vs 12 days; HR, 4.37; 95% CI, 1.86 to 10.24; $P = .001$); 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- β1b, ribavirin, and LPV/r showed faster viral clearance compared with LPV/r only	A
IFN- β [102]	Iran	HCQ + LPV/r or ATV/r, 62% received steroids	RCT, open label	Hospitalized patients with severe COVID-19 with hypoxemia, hypotension, renal failure, neurologic change, thrombocytopenia, or severe gastrointestinal symptoms	Time to clinical improvement	No difference in time to clinical improvement between the groups, 9.7 days for IFN vs 8.3 days ($P = .95$; HR, 1.10; 95% CI, .64 to 1.87); however, day 28 mortality lower in IFN group (19% vs 43.6%, $P = .015$) when adjusted for IVIG and steroid administration effect remained (aHR, 0.375; 95% CI, .16 to .87; $P = .024$)	There were numerically more nosocomial infections in the IFN group (26.2% vs 12.8%, $P = .09$)	In this RCT, IFN- β1a did not increase time to 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	A
IFN-β [103]	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 days vs 11 days; $P = .002$; aHR, 3.41; 95% CI, 1.33 to 8.72)	Nosocomial infections in 3% vs 18% favoring IFN	In this small RCT, IFN-β1b was associated with reduced mortality among a cohort with severe COVID-19; started at mean 7 days of symptom onset	A
IFN-β [18]	Multinational (World Health Organization)	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-β1a was not associated with improved outcomes; there are no data yet available about when in the illness course the treatment was given	A
IFN-α [104]	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 ($P = .002$)	Not reported	In this nonrandomized study, IFN-α2b therapy was associated with more rapid viral clearance from the upper respiratory tract	B
IFN-α [105]	Cuba	LPV/r + chloroquine	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 nonrandomized study where there were significant age and comorbidity differences between the groups, IFN-α2b was associated with improved outcomes	B
IFN-α [106]	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 days vs 15 days, $P = .206$)	Not reported	In this nonrandomized study, IFN-α2b did not have an effect on time to negative upper respiratory tract PCR	B
IFN-α [96]	China	LPV/r or arbidol	Retrospective cohort study	Hospitalized patients with COVID-19 (242)	Mortality	Early IFN therapy was associated with lower mortality (aHR, 0.10; 95% CI, .02 to .50); among the 26 who received late IFN, there was increased mortality (aHR, 2.30; 95% CI, .64 to 8.27 compared with no IFN therapy	Not reported	In this nonrandomized study, early IFN-α2b (defined as given within 48 hours of admission) was associated with reduced mortality	B

Abbreviations: aHR, adjusted hazard ratio; ATV/r, atazanavir with ritonavir; CI, confidence interval; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; HR, hazard ratio; IFN, interferon; IVIG, intravenous immunoglobulin; LPV/r, lopinavir with ritonavir; PCR, polymerase chain reaction; RCT, randomized, controlled trial; Ref, reference.

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

[b]Strength of evidence graded as: A = from a randomized, controlled trial; B = from a nonrandomized study.

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 MERS-CoV Infection Treated with a Combination of Lopinavir-Ritonavir and Interferon Beta-1b (MIRACLE) trial for MERS, which is the first RCT published for treatment of either SARS or MERS, found that interferon-ß1b 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 at 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-β1b, 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 vs 12 days ($P = .001$) [101]. This striking result is notable since no other randomized treatment study has demonstrated such impact, including a remdesivir study [14], and suggests that specific immune augmentation may have a potent anti–SARS-CoV-2 viral effect. Preliminary data from the large World Health Organization–sponsored solidarity trial suggest interferon-ß1b administration was not associated with a change in mortality; however, 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, and further study, particularly early in the disease, is needed. Given the finding of autoantibodies to some type I interferons (most commonly interferon-α) in severe COVID-19, interferon-ß formulations may be more likely to have effect than interferon-α [39].

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 who receive similar salvage chemotherapies without this agent [107, 108]. To date, few published series have reported systematically on the incidence of secondary and nosocomial infections for patients receiving immunomodulatory treatment. Notably, secondary infection rates have not been reported in the RECOVERY trial for dexamethasone [21]. In addition to common nosocomial infections that include bacteremia and pneumonia, case reports document sometimes fatal secondary infections, including from Herpes simplex virus (HSV) reactivation, disseminated strongyloidiasis, and invasive fungal infections [109–112]. Monitoring for reactivation of other latent infections such as hepatitis B and tuberculosis is also critical [113, 114].

Noninfectious complications, including osteonecrosis related to steroids and bowel perforation after IL-6 inhibitor administration, have been noted [115, 116]. 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 [117–119]. 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 [6, 7]. 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 (ie, interferons) may be most likely to show benefit early in the disease course when viral loads are highest, likely within 7 days of symptom onset and sooner if possible. While early hypotheses proposed that the second phase of the 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.

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