Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Hyperinflammation and the utility of immunomodulatory medications in children with COVID-19

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Educational Aims

The reader will come to appreciate that:

- Clinical features of infection with SARS-CoV-2 vary wildly.
- MIS-C presentations include features representative of Kawasaki disease (KD), sepsis, toxic shock syndrome (TSS) and secondary hemophagocytic lymphohistiocytosis (sHLH).
- The concept of antibody dependent enhancement [ADE] has been proposed as a potential etiology for immune complex mediated vasculitis in COVID-19.
- Interleukin related inflammatory response modification holds early promise for treatment of selected severe cases of COVID-19.

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ABSTRACT

The rapid spread of SARS-CoV-2 infection globally coupled with the relatively high case-fatality rate has led to immediate need for therapeutic intervention to prevent and treat COVID-19 disease. There is accumulating evidence that morbidity and mortality in COVID-19 may be exacerbated by a dysregulated host immune response resulting in significant hyperinflammation and cytokine release. The aim of this review is to describe the basis for the immune dysregulation caused by SARS-CoV-2 infection and to examine current investigations into immunomodulatory therapies aimed at targeting the excessive host immune response.

INTRODUCTION

In December 2019, an outbreak of a novel coronavirus, designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly throughout Wuhan, China and subsequently around the world. Similar to prior novel coronavirus infections (SARS and MERS), infection with SARS-CoV-2 leads to a severe pneumonia and acute respiratory distress syndrome (ARDS) in a subset of patients. In February 2020, the World Health Organization (WHO) designated the disease associated with SARS-CoV-2 as COVID-19. Mortality in patients with COVID-19 is highest in patients with ARDS admitted to intensive care units and is often exacerbated by a dysregulated immune response leading to significant hyperinflammation and cytokine release.

Until recently, children were thought to be spared more severe manifestations. In April 2020, an unanticipated inflammatory syndrome related to COVID-19 rapidly emerged in children. This entity has now been termed multi-system inflammatory syndrome in children (MIS-C) by the Centers for Disease Control (CDC) (also known as pediatric multi-system inflammatory syndrome (PMIS)). Since first described in the United Kingdom in April 2020, there has been a rapid increase in reported cases in several other countries. Presentations of MIS-C are variable, with features representative of Kawasaki disease (KD), sepsis, toxic shock syndrome (TSS) and secondary hemophagocytic lymphohistiocytosis (sHLH). It is unknown to what extent patients affected with MIS-C have pathophysiology similar to these known clinical entities and to what extent they might respond to typical medications used in these conditions.

The rapid spread of SARS-CoV-2 infection globally and the relatively high case-fatality rate has led to immediate need for therapeutic intervention to prevent and treat COVID-19 disease. Many

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agents are currently under investigation in an effort to target different pathways of viral infection and host response. This review aims to describe our current understanding of the hyperinflammatory response and the immunomodulatory targets. We will review the existing data, with the acknowledgment that new information becomes available every day and may not be included within the timeframe of this review.

HOST INFLAMMATORY RESPONSE TO SARS-COV-2 INFECTION

Hyperinflammation and cytokine storm

The proposed mechanism of severe infection with SARS-CoV-2 has been sub-divided into the viral replication phase and the hyperinflammatory phase. These phases correspond to three clinical stages: early infection, pulmonary phase, and hyperinflammatory phase [1]. During viral replication, SARS-CoV-2 infects airway epithelial cells through interactions with the transmembrane enzyme ACE2 [2]. The virus evades innate immune response by suppressing early pro-inflammatory responses through type I interferons (IFN) and pro-inflammatory effector cytokines (IL-1, IL-6 and TNF-α). Infected cells undergo cell death and release virus particles together with intracellular components, which trigger innate immune activation and expression of pro-inflammatory cytokines. Stimulated monocytes/macrophages and neutrophils exhibit strong and poorly controlled inflammatory reaction, resulting in tissue damage and systemic inflammation. This, in turn, leads to activation of the adaptive immune system likely driven by T lymphocytes [2].

Evidence of immune dysregulation in SARS-CoV-2 infection shares similar features to conditions associated with "cytokine storm". This umbrella term is used to describe the immune system response to a stimulus with a dysregulated and excessive release of inflammatory molecules, resulting in organ dysfunction and damage. Cytokine storm syndromes include various entities, depending on the inciting factor: primary Hemophagocytic Lymphohistiocytosis [HLH] in children with specific genetic mutations; secondary HLH due to infection or malignancy, macrophage activation syndrome due to rheumatologic disease and cytokine release syndrome (CRS) when hyperinflammation is due to CAR T-cell therapy. All of these conditions have common clinical and laboratory characteristics, such as fever, hypotension, rash, liver dysfunction, elevated ferritin, cytopenias, low fibrinogen, high markers of inflammation and elevated pro-inflammatory cytokines (particularly IL-6 and IL-18). Features of cytokine storm in COVID-19 are usually evident in the second week of illness.

While there are common findings between SARS-CoV-2 cytokine storm and viral induced sHLH, there are also a few striking differences. One of the most important differences is that ferritin is only modestly elevated in SARS-CoV-2 inflammatory state, whereas significant hyperferritinemia is a defining feature in sHLH. In addition, the predilection for severe respiratory involvement is more predominant in cytokine storm secondary to SARS-CoV-2 [3]. Furthermore, fibrinogen (often low in sHLH) is consistently elevated in severe SARS-CoV-2 infection and in contrast to the leukopenia seen in sHLH, severe COVID-19 infection is associated with leukocytosis [4]. Other features of sHLH such as hypertriglyceridemia, splenomegaly, hepatomegaly, bone marrow hemophagocytosis have yet to be described in cohort studies of COVID-19.

Immune complex mediated inflammatory response

Another proposed mechanism for hyperinflammation secondary to SARS-CoV-2 infection includes the concept of antibody-dependent enhancement (ADE). ADE is a phenomenon occurring in viral infections, in which early neutralizing antibodies promote cellular uptake of virus particles bound in immune complexes, through their binding to Fcγ receptors. This process contributes to persistent viral replication in immune cells, as well as immune complex mediated inflammatory response, leading to end organ damage such as ARDS [2]. ADE has been classically described in infection with Dengue virus, in which patients re-infected with a different serotype of the virus run a more severe course of infection [5]. In COVID-19, it has been hypothesized that ADE might play a role in severe infection in patients previously infected with other coronaviruses, including agents of the common cold and SARS-CoV [5].

The concept of ADE has been proposed as the potential etiology for clinical manifestations reported in COVID-19 including immune complex mediated vasculitis, manifesting as vasculitic skin lesions, small vessel microthrombi and infarctions. Histopathologic features are consistent with immune complex mediated vasculitis, with the infiltration of monocytes and lymphocytes in and around blood vessels, wall thickening, and focal hemorrhage [2]. The presence of acral perniosis, or chilblains, in both adult and pediatric patients with SARS-CoV-2 infection seems to be additional evidence for inflammatory vasculitis [6]. Although still under investigation, ADE has been proposed as a potential mechanism underlying the newly described MIS-C, based on the observation that a majority of the patients have evidence of existing antibodies to SARS-CoV-2 and the inflammatory condition seems to lag behind the COVID-19 infection peak by approximately 4–6 weeks.

Clinical features of COVID-19 disease

Clinical features of infection with SARS-CoV-2 vary wildly. In a report of the largest case series to date of COVID-19 in Mainland China reported by the Chinese Center for Disease Control, 81% of patients had mild disease, 14% severe and 5% critical [7]. Common symptoms at presentation include fever, cough, sore throat, myalgia or fatigue, sputum production [8,9]. Similarly, an observational cohort study from the United States (US) describes shortness of breath, fever and cough as the most common presenting symptoms of patients hospitalized with COVID-19 infection [10]. Of the 1150 admitted patients in this cohort, 257 (22%) were critically ill and 212 (82%) had at least another chronic illness.

Multiple studies have analyzed risk factors for severe disease in COVID-19 infection and showed evidence that hyperinflammation (elevated levels of ferritin, D-dimer, LDH, IL-6 and lower lymphocyte count) was seen in patients with severe disease, as well as non-survivors [8,11,12]. Chen G et al described markedly higher levels of IL-2R, IL-6, IL-10, and TNF-α and lower T lymphocytes (both CD4 and CD8+) in patients with severe COVID-19 [13]. Similarly, two meta-analyses have shown that patients with severe/-critical disease were characterized by low lymphocyte counts (especially T lymphocytes), high markers of inflammation (C-reactive protein (CRP), ESR, IL6, procalcitonin), elevation in liver enzymes, abnormal coagulation and kidney function, as well as elevation in biomarkers of myocardial function (including troponin and creatine kinase) [14,15].

To date, most cases of COVID-19 in children were thought to be asymptomatic or have mild presentation. In a systematic review of 18 studies in China with 1065 participants, children at any age were found to be asymptomatic or present with mild respiratory symptoms, namely fever, dry cough, and fatigue [16]. Similarly, Dong et al reported a Chinese nationwide case series of 2135 patients with COVID-19 [17]. Most patients (>90%) were asymptomatic or had mild-moderate cases. Infants were found to be more likely to be severely affected. Almost all children recovered, with only one fatality reported. Chilblains have also been described in both children and adults. Two small series from Italy and the US

describe cases of acral purpura in children either diagnosed with, or with strong suspicion for, COVID-19 [18,19]. All pediatric cases described seemed to have a relatively mild form of viral infection. This was hypothesized to be due to a robust type I IFN response after viral exposure which may both protect from progressive infection and precipitate inflammatory perniosis through the same pathway [19].

In contrast, recently published data from the US describe a subgroup of pediatric patients with severe disease. Chao et al and DeBiasi et al report data from two major epicenters of disease in the US, including pediatric patients admitted to hospitals in NY and Washington, DC [20,21]. Of these patients, 28% and 20% of patients respectively were found to have severe disease, with a need for respiratory support. In NY, admission to the intensive care unit was associated with higher levels of CRP, procalcitonin, pro-BNP and platelet levels [20]. In the DC cohort, the age for critically ill children was considerably higher compared with non-critically ill patients.

Multisystem inflammatory syndrome in children

MIS-C appears to have a clinical spectrum of disease, broadly divided into two subsets of patients: (1) those that present with classic or atypical KD features, including reports of dilated coronary arteries and (2) those that present with a phenotype of sepsis, cardiovascular shock or cardiac dysfunction. In contrast with adults and children from initial COVID-19 cohorts, most of these children do not have underlying medical conditions. A slight male predominance has been described, with median ages reported between 7.5 and 10 years old (Table 1) [22–25]. Supportive clinical features described include persistent fever >38.5 C, variable rash, conjunctivitis, peripheral edema, severe abdominal pain and diarrhea. Interestingly, respiratory distress does not seem to be one of the main presenting symptoms, although a proportion of patients do require respiratory support. More significantly, a large percentage of these children present with hypotension and shock. Echocardiogram findings include ventricular dysfunction and coronary artery abnormalities. Patients with MIS-C also have evidence of severe inflammatory state, with elevation in CRP, ferritin, D-dimer, LDH, pro-BNP and cardiac enzymes. Patients may additionally have elevated procalcitonin, liver transaminases, anemia, along with either thrombocytopenia or thrombocytosis [22,23]. Fortunately, most children with MIS-C have recovered, however few deaths have been reported [22]. Although some children are SARS-CoV-2 PCR positive, most are PCR negative and IgG antibody positive, supporting the hypothesis that MIS-C might represent a delayed inflammatory process.

TREATMENT FOR HYPERINFLAMMATION ASSOCIATED WITH SARS-COV-2 INFECTION

Corticosteroids

The use of steroids in treatment of SARS-CoV-2 is controversial. Steroids suppress lung inflammation and cytokine storm but can also increase secondary infection rate and delay viral clearance. Steroids are recommended by Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) for patients with early moderate to severe ARDS [26]. For treatment of sepsis and septic shock, corticosteroids may be used in patients refractory to fluid and vasopressor therapy, however guidelines emphasize using low dosages and short-term application [27]. Steroids were the main immunomodulatory medication used during the 2003 SARS epidemic, however later studies did not show beneficial effects and delayed viral clearance. Similarly, a review by Russel et al. [28], showed no evidence of benefit for use of corticosteroids in MERS, SARS, influenza or RSV.

Studies about steroid use in COVID-19 infection are also mixed. Chen et al. [29] reported use of steroids in 19 (19%) of their cohort and recommend it for patients with ARDS for as short a duration as possible. Similarly, Wu et al [30] described that the administration of methylprednisolone appears to have reduced the risk of death in patients with ARDS (HR, 0.38; 95% CI, 0.20–0.72; $P = 0.003$) and Wang et al. [31] reported that patients receiving intravenous methylprednisolone at a dose of 1–2 mg/kg had shorter duration of oxygen supplementation (8.2 days vs. 13.5 days; $p < 0.001$). In contrast, Wang et al. [32] described a cohort study in which the 45% of patients receiving methylprednisolone demonstrated "no effective outcomes" and Zhou et al. [33] reported on 15 patients with moderate-severe ARDS potential benefit with corticosteroids but no improvement in overall survival. Zhou et al. [33] discuss the role of corticosteroids in severe COVID-19 infection based on observations of early cases from Wuhan and recommend short duration and lower dose treatment (<1 mg/kg body weight, up to 7 days) for severely ill patients [33]. Current NIH recommendations are against routine use of systemic corticosteroids in hospitalized patients unless they are in ICU, as well as against use in mechanically ventilated patients without ARDS. For patients that are mechanically ventilated with ARDS, NIH states that there is insufficient evidence for or against use of corticosteroids. The role of corticosteroids in children with COVID-19 or MIS-C has yet to be fully elucidated.

Interleukin 6 (IL-6) blockade

Interleukin 6 (IL-6) is a soluble factor secreted by T lymphocytes, shown to be important for antibody production by B cells, as well as activation of both local and systemic inflammatory pathways [34]. IL-6 binds to a membrane receptor or a soluble receptor and leads to gp130 dimerization, phosphorylation, and activation of receptor-associated kinases [35]. This pathway plays a role in the pathogenesis of several rheumatic diseases, and blockade of IL-6 has proven to be a successful therapeutic intervention in rheumatoid arthritis (RA), juvenile idiopathy arthritis (JIA), adult-onset Still's disease (AoSD), Takayasu arteritis (TA) as well as other conditions including CRS secondary to CAR-T cell therapy. Multiple monoclonal antibodies have been developed, with those that block the IL-6 receptor (tocilizumab, sarilumab) most frequently studied in COVID-19. Most safety concerns with IL-6 receptor blocker show reversible elevation of liver enzymes, pancreatitis, risk for GI perforation and risk for serious bacterial or fungal infections. The rationale for use of IL-6 blockade in serious COVID-19 infections is based on the observation that for the subset of patients with severe manifestations, IL-6 is most likely one of the drivers of the cytokine storm, and elevated levels of IL-6 have been consistently shown [14]. Tocilizumab was one of the first anti-inflammatory agents trialed and multiple clinical trials in IL-6 blockade are ongoing globally.

Current data for IL-6 blockade in COVID-19 is limited to adults but has overall been promising. In the earliest tocilizumab study, Xu et al reported improvement in all 21 patients receiving tocilizumab, however this was a small single arm study with no control group [36]. Two additional studies from France showed significant improvement in patients treated with tocilizumab with reduced rate of ICU admission and risk for mechanical ventilation, however there was no significant reduction in mortality [37,38]. Additional studies have shown mixed results (Table 2) [39–42]. At the time of this review, the largest trial to date is the Sanofi/Regeneron phase 2/3 Sarilumab trial. In this trial, 457 hospitalized patients were categorized as having either "severe" illness (28%), "critical" illness (49%) or "multi-system organ dysfunction" (MSOD) (23%) [43].

Table 1
Clinical characteristics, lab parameters, therapies and outcomes of patients with MIS-C.*

Source	Study region	Riphagen et al (n = 8) UK	Verdoni et al (n = 10) Italy	Toubiana et al (n = 17) France	Belhadjer et al (n = 35) France and Switzerland
	Study period	10 days in mid-April 2020	Feb 18–April 20, 2020	April 27–May 7, 2020	March 22–April 30, 2020
Clinical characteristics	Age in years	8 [4–14]	7.5 [2.9–16]	7.5 [3.7–16.6]	10 [2–16]
	Male gender	5 (62)	7 (70)	7 (41)	18 (51)
	Comorbidities**	2 (25)	1 (10)	-	10 (28)
	Fever	8 (100)	10 (100)	17 (100)	35 (100)
	Gastrointestinal symptoms***	7 (88)	6 (60)	17 (100)	29 (83)
	Met criteria for KD	–	5 (50)	8 (47)	0 (0)
	Incomplete KD	–	5 (50)	9 (53)	35 (100)
	Hypotension/shock	8 (100)	5 (50)	11 (65)	28 (80)
	Mechanical ventilation	7 (88)	-	10 (59)	23 (66)
	Left ventricular dysfunction	6 (75)	6 (60)	12 (71)	28 (80)
	Coronary artery abnormalities (dilation, aneurysms)	2 (25)	2 (20)	8 (47)	6 (17)
	Abnormal CXR with pulmonary infiltrates	–	5 (50)	6 (43)	–
Significant labs****	CRP (mg/dL)	30.1 [16.1–55.6]	24.1 [7.5–52.5]	21.9 [8.9–36.3]	24.1 [15–31.1]
	Procalcitonin (ng/mL)	11.6 [7.4–71.5]	-	23.3 [0.1–448]	36 [8–99]
	NT-proBNP (ng/L)	13,427 [7000–>35,000]	1235 [108–2957]	2879 [16–16,017]	41,484 [35,811–52,475]
	Troponin (ng/L)	83.5 [25–675]	111 [2.9–4906]	136 [10–6900]	347 [186–1267]
	D-dimer (ng/mL)	10,500 [3400–24,500]	3798 (SD1318]	4762 [350–19,33]	5284 [4069–9095]
	Ferritin (ng/mL)	602 [277–4220]	893 [199–3213]	–	–
	SARS-CoV-2 NP PCR	0	2 (20)	7 (41)	12 (34)
	SARS-CoV-2 antibodies	8 (100)	8 (80)	14 (88)	30 (86)
Treatments	Inotropes	8 (100) ECMO *n* = 1	2 (20)	10 (59)	28 (80) ECMO *n* = 10
	IVIG	8 (100)	10 (100)	17 (100) 2nd dose *n* = 5	25 (71) 2nd dose *n* = 1
	Aspirin	6 (75)	2 (20)	17 (100)	-
	Corticosteroids	4 (50)	8 (80)	5 (29)	12 (34)
	Other	1 (infliximab)	0	0	3 (anakinra)
Outcome	Death	1	0	0	0

*Continuous variables are expressed as median [range]; categorical variables are expressed as numbers (percentage).
** Comorbidities include asthma, obesity, lupus, autism, ADHD.
*** Gastrointestinal symptoms include abdominal pain, vomiting, diarrhea.
**** Reference ranges may vary per study and laboratory.
– Data not reported.
CRP: C-reactive protein; NT-proBNP: N-terminal pro hormone brain natriuretic peptide; NP PCR: nasopharyngeal PCR.

Patients were classified as "severe" if they required oxygen supplementation without mechanical or high-flow oxygenation; or "critical" if they required mechanical ventilation or high-flow oxygenation or required treatment in an intensive care unit. The trial met its primary endpoint of CRP reduction and demonstrated no new safety concerns. There is caution not to overinterpret the results of this trial, in that, reduction in CRP is an expected outcome of treatment with IL-6 blockade and thus may have not been an ideal primary endpoint. An exploratory analysis of outcome (clinical status, mortality, discharge), showed negative trends for outcomes in "severe" group, and positive trends for outcome in "critical" group. Ongoing phase 3 trial is currently enrolling internationally.

Interleukin 1 (1L-1) blockade

Interleukin 1 is one of the primary cytokines involved in hyperinflammation and has a fundamental role in the development of cytokine storm in sHLH. Anakinra is a recombinant IL-1 receptor antagonist originally developed to control sepsis-induced cytokine storm and subsequently used in cytokine storm induced by a variety of conditions. It is currently FDA approved for treatment of RA, Systemic JIA, Still's disease and cryopyrin-associated periodic syndromes and used off-label for cytokine storm syndromes with accumulating evidence of its benefit in controlling hyperinflammation [44]. A perceived advantage of using anakinra for IL-1 blockade is its short half-life, with high dose regimens shown to be safe, even in context of sepsis [3,45].

In COVID-19 infection, IL-1 blockade has been hypothesized to play a significant role in controlling hyperinflammation [2,46,47]. IL-1α is released by dying epithelial and endothelial cells, whereas IL-1β is produced by infiltrating monocytes, macrophages, and neutrophils [46]; both major factors contributing to hyperinflammation. To date, the data on IL-1 blockade in COVID-19 infection is scarce but encouraging, with multiple clinical trials currently in progress. Cavalli et al [46] describe a retrospective cohort study of 36 adult patients treated with anakinra (7 patients received 'low-dose' 100 mg subcutaneously BID and 29 patients received 'high-dose' 5 mg/kg intravenously BID). The authors report that treatment with low-dose anakinra demonstrated no benefit at 7 days and was discontinued, however treatment with high-dose anakinra resulted in higher survival rate at 21 days (cumulative survival of 90% in the anakinra group versus 56% in the standard treatment group ($p = 0.009$)).

Pontali et al [48] also described early treatment with high dose IV anakinra (100 mg IV every 8 h) for 5 patients with COVID-19 and

Table 2
Treatment of COVID-19 with IL-6 inhibitors.

Source	Xu, X et al., 2020	Luo et al., 2020	Gritti et al., 2020	Toniati et al., 2020	Klopfenstein et al., 2020	Roumier et al., 2020
Country of origin	Anhui, China	Wuhan, China	Bergamo, Italy	Brescia, Italy	Nord Franche-Comté, France	Suresnes, France
Center	Single center	Single center	Single center	Single center	Single center	Single center
Study period	February 5–14, 2020	January 27–March 5, 2020	March 11–24, 2020	March 9–20, 2020	April 1–13, 2020	March 21–April 2, 2020
Type of study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective series	Retrospective case-control	Retrospective case-control
Number of patients	21	15	21	100	20 TCZ 25 Standard therapy (ST)	30 TCZ 29 Standard therapy
Age in years ¥	56.8 ± 16.5	73 (62–80)	64 (48–75)	62	76.8 ± 11 in TCZ group 70.7 ± 15 in ST group	50
Male gender (%)	86	80	86	88	–	80
Follow up (days)	–	7	8	10	–	8 (6.0–9.75)
Inclusion criteria and ICU status, if reported	Severe: tachypnea and/or respiratory failure 17 (81%) Critical: mechanical ventilation or organ support on ICU 4 (19%)	Moderately, severely or critically ill (not otherwise specified)	All required either CPAP or NIV	NIV 57 (57%) or mechanical ventilation 43 (43%) 43 in ICU 57 in general ward (because no ICU beds available)	Failure of standard treatment, time to symptoms onset >7 days, O2 therapy ≥5 L/min, >25% lung damage on CT, ≥2 elevated markers of inflammation TCZ group: more lung involvement on CT, lymphopenia, high CRP, higher level O2 therapy None in ICU at enrollment (ICU admission was one of the outcomes)	Severe (O2 requirement >6 L/min, rapidly deteriorating, high CRP, with ≥5 days of prior disease duration. 7 (23%) in ICU
IL-6 agent and dose	TCZ 4–8 mg/kg body weight, recommended dose 400 mg maximum 800 mg. 14.3% received 2nd dose 12 hours later	TCZ 80–600 mg 33% administered subsequent doses	Siltuximab median dose 900 mg × 1 for all 21; 5 patients received a second dose	TCZ 8 mg/kg (max 800 mg) by two consecutive intravenous infusions 12 hours apart Eighty-seven patients (87%) received 2 infusions of TCZ, 13 patients (13%) 3 infusions	TCZ 1 or 2 doses (dose not reported)	TCZ 8 mg/kg
Other treatments	Lopinavir/Ritonavir Interferon-α Methylprednisolone	8 (53%) also received methylprednisolone	Usual care (not specified)	Lopinavir/ritonavir or remdesivir antibiotics ppx, hydroxychloroquine 400 mg and dexamethasone 20 mg/day	hydroxychloroquine or lopinavir-ritonavir therapy and antibiotics, and less commonly corticosteroids	2 patients in TCZ group also received 10 day course HCQ and azithro; 2 patients in control group received high dose methylprednisolone pulses
Outcome	All 21 discharged from hospital	10 (67%) stabilized 2 (13%) worsening disease 3 (20%) died Median CRP fell from 126.9 to 11.2 m g/L Drop in IL-6 in 67%	7 (33%) improved 9 (43%) stabilized 5 (24%) worsened and required intubation	*General wards patients:* 37 (65%) improved 7 (12%) stabilized 13 (23%) patients worsened *ICU patients:* 32 (74%) improved 1 (2%) stabilized 10 (24%) died *Overall at 10 days:* 77 (77%) improved/ stable 23 (23%) worsened 20 (20%) died *Note:* 3 patients had GI perforation requiring urgent surgery	*TCZ group:* 3 (15%) remained hospitalized 11 (55%) discharged 5 (25%) death and/or ICU *ST group:* 2 (8%) remained hospitalized 8 (32%) required invasive mechanical ventilation; 11 (44%) discharged 18 (72%) death and/or ICU admission 12 (48%) death	*TCZ group:* 4/7 (57%) discharged from ICU 6/30 (20%) discharged from hospital 3 (10%) death TCZ significantly reduced requirement of subsequent mechanical ventilation (weighted OR: 0.42; 95%CI [0,20–0,89] p = 0,025) TCZ significantly reduced ICU admission (weighted OR: 0.17; 95%CI [0,06–0,48] p = 0,001)

¥ Values expressed as mean or median according to original report.
– Data not reported.
TCZ Tocilizumab.

severe lung involvement. All five patients had rapid resolution of systemic inflammation and remarkable improvement in respiratory status, with no adverse effects seen.

Intravenous immunoglobulin (IVIG)

Use of immunoglobulins is another potential adjunctive therapy for COVID-19. The rationale for use of hyperimmune immunoglobulins or intravenous immunoglobulins (IVIG) is that the high IgG levels in serum help block Fcγ receptors, neutralize pathogens in respiratory tract, block receptors associate with target cells, as well as influence lymphocyte differentiation and maturation [2,49]. In addition, IVIG has been proposed to inhibit cytokine production and function (particularly IL-1 and IL-6). This treatment has been studied in other viral infections, including influenza, SARS and MERS, with reported reduction in mortality, however study quality was low with risk for bias [50].

Data in COVID-19 is limited. Xie et al describe a retrospective study of 58 cases of severe or critical patients treated with IVIG (in addition to standard therapy) either within 48 hours from admission or after 48 hours [49]. Patients in the early treatment group were found to have significant improvement in 28 days mortality ($P = 0.009$), decreased length of stay ($p = 0.0055$), length of stay in ICU ($p = 0.0453$) and need for mechanical ventilation ($p = 0.016$). IVIG has been considered for the treatment MIS-C given the similarity in features with Kawasaki disease (KD). Since IVIG is standard treatment for KD, IVIG has been used for treatment of MIS-C in most reports to date, in combination with other agents such as corticosteroids and aspirin (Table 1).

Convalescent plasma

Passive immunization can also be applied through use of convalescent plasma. This treatment modality has been trialed since early 20th century for infections with 'Spanish flu' Influenza A (H1N1), SARS-CoV, West Nile virus and Ebola, with mixed effect. Some studies found benefit in influenza and SARS infection when administered early in the course of the disease, however no similar response was found in Ebola virus disease [51]. Importantly, convalescent plasma has been shown to be safe when administered in infection with multiple viruses including influenza, SARS, MERS, Ebola and SARS-CoV-2 [51]. Convalescent plasma contains both neutralizing antibodies to the viral infection as well as other protective antibodies including IgG, IgM, anti-inflammatory cytokines; it plays a role in both anti-viral mechanisms as well as multiple mechanisms of immunomodulation. Multiple convalescent plasma trials in COVID-19 are currently ongoing.

Janus kinase inhibitors

The JAK/STAT pathway is the principal signaling mechanism for a wide array of cytokine and growth factors, and JAK activation stimulates cell proliferation, differentiation, migration and apoptosis [52]. This pathway is thought to be used by SARS-CoV-2 host cells, mainly lung cells which express ACE2 and AP2-associated protein kinase 1 (AAK1) (a regulator of endocytosis). Reports suggest that blocking AAK1 may interrupt viral entry into cells and thus decrease the viral proliferation phase [53]. A second mechanism by which the JAK/STAT pathway contributes to COVID-19 pathogenesis is through cytokine release. Interferons α and β and IL-6 all signal through the JAK/STAT pathway, thus inhibiting JAK/STAT activation could lead to dampening of the cytokine storm. JAK inhibitors have been suggested for treatment of COVID-19 [54,55], although some authors caution against its use. Concerns regarding the use of JAK inhibitors include cytopenias, elevation of creatine kinase, risk for infection [56], risk for thrombosis and the fear of inhibiting interferon-mediated anti-viral response, with potential facilitating effect on COVID-19 infection [57].

There are a number of JAK inhibitors currently in use, mostly in rheumatic and dermatologic conditions. Baricitinib is an oral selective JAK 1 and 2 inhibitor which is FDA approved for RA and has also been used in interferonopathies. A small pilot study from Italy [58] showed that baricitinib at 4 mg/day/orally (combined with lopinavir-ritonavir) was safe in 12 patients with moderate COVID-19 pneumonia, with significant improvement in clinical and respiratory parameters at 2 weeks**.** Ruxolitinib, another JAK 1 and 2 inhibitor, was recently reported to be safe and show a numerically faster improvement in clinical symptoms in 20 patients with severe COVID-19, although this was not statistically significant [59].

Other agents

Other agents currently under investigation for their role in treating COVID-19 associated hyperinflammation are emapalumab (an Anti-IFNγ Monoclonal Antibody), colchicine, complement C3 inhibitor AMY-101.

CONCLUSION

Infection with the novel coronavirus SARS-C0V-2 represents the greatest public health crisis of our generation. This is due to the fact that there is no existing immunity and a significant proportion of the population develops severe disease. The virus seems to behave in new and unexpected ways, as evidenced by the presentation of MIS-C, which has not been previously described with other coronavirus infections. Much work is needed to develop evidence-based, therapeutic manipulation of the inflammatory response resulting from severe infection with SARS-CoV-2. This is desperately needed now, in the period before a safe and efficacious vaccine can be developed.

DIRECTIONS FOR FUTURE RESEARCH

We are currently only starting to understand the underlying immune mechanisms activated by infection with SARS-CoV-2, as well as host factors that contribute to severity of disease. Further understanding of these complex immune responses will play a role in formulation of effective therapeutic interventions.

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