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Review

Emerging trends in COVID-19 treatment: learning from inflammatory conditions associated with cellular therapies



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ABSTRACT

Coronavirus disease 2019 (SARS-CoV2) is an active global health threat for which treatments are desperately being sought. Even though most people infected experience mild to moderate respiratory symptoms and recover with supportive care, certain vulnerable hosts develop severe clinical deterioration. While several drugs are currently being investigated in clinical trials, there are currently no approved treatments or vaccines for COVID-19 and hence there is an unmet need to explore additional therapeutic options. At least three inflammatory disorders or syndromes associated with immune dysfunction have been described in the context of cellular therapy. Specifically, Cytokine Release Syndrome (CRS), Immune Reconstitution Inflammatory Syndrome (IRIS), and Secondary Hemophagocytic Lymphohistiocytosis (sHLH) all have clinical and laboratory characteristics in common with COVID19 and associated therapies that could be worth testing in the context of clinical trials. Here we discuss these diseases, their management, and potential applications of these treatment in the context of COVID-19. We also discuss current cellular therapies that are being evaluated for the treatment of COVID-19 and/or its associated symptoms.

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Coronavirus disease 2019 (COVID-19) is an infectious illness caused by a novel betacoronavirus strain first recognized in December 2019. The etiological agent of COVID-19, SARS-CoV2, is structurally related to viruses responsible for severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These coronavirus strains have been responsible for epidemics and high fatality rates in the past two decades. COVID-19 is an active global health threat with conflicting fatality rate reports, but it is known to be higher in hosts with preexisting medical conditions and/or advanced age [1].

At the time of this writing, COVID-19 pandemic continues unabated in many parts of the globe. Although most people infected with SARS-CoV2 experience mild to moderate respiratory symptoms and recover with supportive care, certain hosts (even including younger, previously healthy ones) are more likely to develop a precipitous

clinical decline. Current data support that hyperimmune host reactions triggered by the virus are at least partially responsible for these poor outcomes [2]. Early identification and intervention in these high-risk patients may provide a means to disease amelioration and potentially expedited recovery, although to date no pharmacological therapy has been identified.

A full-bodied worldwide research effort is currently underway to repurpose existing drugs and develop new therapies able to halt progressive disease that leads to respiratory failure and death. Here, we explore how we can apply our extensive knowledge of immune modulation that has been gained from the cellular therapy field to overcome the therapeutic challenges of treating COVID-19. Biological therapies to dampen hyperimmune host responses could potentially be implemented along with supportive care (supplementary oxygen and mechanical ventilatory support when indicated) or in combination with other pharmacotherapies such as antimalarials, antivirals, anti-COVID-19 antibody infusions (convalescent serum), anticoagulation and immunization.

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COVID-19 pathophysiology

SARS-CoV2 is a betacoronavirus closely related to SARS-CoV. Both viruses use the angiotensin-converting enzyme–related carboxypeptidase (ACE2) receptor to gain entry to cells. This receptor is widely expressed in cardiopulmonary tissues and also in some hematopoietic cells, including monocytes and macrophages [3]. Direct diffuse alveolar damage due to viral targeting of the human respiratory tract epithelium via ACE2 receptors may lead to a hyperimmune response in the host, which can result in the development of acute respiratory failure and ultimately, in some cases, death. Decade-long structural studies on SARS-CoV postulate that viral receptor recognition is one of the most important determinants of its cross-species and human-to-human transmissions, strongly suggesting that SARS-CoV2 uses ACE2 as its receptor [4]. Recently, a cohort of 21 patients with confirmed COVID-19 infection and severe disease showed markedly elevated blood levels of cytokines and chemokines that may predict disease severity [5]. This virus-induced exaggerated host immune response is a previously described phenomenon thought to be responsible for the high fatality rate observed in healthy young adults during the 1918 influenza pandemic and also described with SARS and MERS infections [6].

Early clinical reports of malaise, high fever, chills, anosmia, dysgeusia and hypoxia combined with biochemical markers associated with inflammation and hypercoagulable state seem to be prevalent. Laboratory anomalies such as lymphopenia, high ferritin, elevated lactate dehydrogenase, interleukin (IL)-6, high C-reactive protein and soluble CD25 suggest that SARS-CoV-2 infection may trigger cytokine storm syndrome. This hyper-reactive cytokine release may represent one of the most important negative prognostic factors in patients infected with COVID-19. Interestingly, these responses resemble inflammatory conditions not infrequently seen after hematopoietic stem cell transplant (HCT) and cellular therapies: cytokine release syndrome (CRS), immune reconstitution inflammatory syndrome (IRIS), and secondary hemophagocytic lymphohistiocytosis (sHLH).

Inflammatory conditions associated with cellular therapies

Three prominent immune dysregulation syndromes that may arise after cellular therapy and stem cell transplantation include CRS, sHLH and IRIS. All three have clinical and laboratory characteristics in common and with patterns described in patients with severe COVID-19 (Table 1). These immune responses may be fatal if not recognized and treated promptly.

CRS is a potentially life-threatening, non–antigen-specific toxicity that has been described following use of bispecific antibodies such as blinatumomab, chimeric antigen receptor (CAR)-T cell therapy and other immune therapies including but not limited to anti-thymocyte globulin (ATG) rituximab, alemtuzumab and nivolumab. CRS is one of the two most common treatment-related adverse events observed after CAR-T cell therapy; as such, identification, grading and treatment of this complication has been well described in recent years [7,8]. To harmonize the definitions and grading systems for CRS and neurotoxicity, consensus recommendations were recently implemented by the American Society for Transplantation and Cellular

Therapy [9] (Table 3). The clinical manifestations of CRS have variable timing and can range from mild to life-threatening. The onset of CRS may be within hours after therapeutic antibody therapy and resolve within days. In contrast, the typical course of CRS after CAR-T infusion, is 1 to 14 days (median, 2–3 days), and resolution is expected within a few days to weeks. CRS manifests with fever, tachycardia, hypotension, respiratory distress or hypoxemia and is associated with elevated circulating levels of several cytokines including IL-6 and interferon- γ [9]. In general, the degree of cytokine activation correlates with the severity of the clinical picture. Other laboratory findings are variable and reflect systemic inflammation. sHLH/macrophage activation syndrome (MAS) is a syndrome of excessive inflammation and tissue destruction with overlapping features of CRS. In adults, sHLH is most commonly triggered by viral infections. sHLH is characterized by T-cell-mediated inflammation, fulminant cytokine storm, ferritin elevation and multi-organ failure. The HLH diagnostic criteria is based on the HLH Study Group of the Histiocyte Society 2004 description of the combination of five of the following eight characteristics (Table 2): fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, high ferritin, hemophagocytosis, low/absent NK-cell activity and high soluble IL-2 receptor. CRS and sHLH/MAS have many features in common, as each reflects the activation of the reticuloendothelial system initiated by T-cell-mediated inflammation. In the CAR-T literature, most patients with moderate to severe CRS meet criteria for HLH/MAS with or without organomegaly, lymphadenopathy or evident hemophagocytosis. Patients may meet some of the criteria for HLH/MAS after CAR-T-cell infusion, but this may also reflect CRS [9]. Importantly, the clinical and cytokine profile suggestive of HLH/MAS resolve with CRS resolution; therefore, primary amelioration of CRS with targeted cytokine biologics may be sufficient without using specific HLH pharmacotherapies [10]. A retrospective study of COVID-19 patients found that elevated serum ferritin and IL-6 correlated with increased mortality [2].

IRIS is another hyperinflammatory syndrome with pathogenesis dependent on CD4⁺ T cells, proinflammatory cytokines, macrophages and other innate immune cells. IRIS is a phenomenon described in human immunodeficiency virus (HIV) patients with severe lymphopenia and underlying opportunistic infections, occurring during immune recovery upon initiation of antiretrovirals and presenting as

Table 2
HLH diagnostic criteria.

HLH
Fever >38.5
Splenomegaly
Cytopenia in at least 2 lineages (Hb <9 g/dL, platelets <100 000/mm ³ , ANC <1000/mm ³)
Hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
Hemophagocytosis in bone marrow, spleen, lymph node or liver
Low or absent NK activity
Ferritin >500 ng/mL
Elevated soluble CD25 (soluble IL-2 receptor alpha) 2SD above age-adjusted lab specific norms (>2400 IU/mL)

The eight diagnostic criteria according to HLH-2004 trial: at least five of eight criteria must be present to make the diagnosis of HLH

Table 1
Comparison of clinical features of COVID-19 and other hyperimmune response syndromes.

	Fever	Hypoxia	Hypotension	Cytokine storm	Cytopenias	Ferritin	Hypofibrinogenemia	Organomegaly
CRS	+	+	+	+	+/-	+/-	+/-	+/-
IRIS	+	+	+/-	+	-	+/-	+/-	+/-
sHLH	+	+/-	+/-	+	+	↑	+	+
COVID-19	+	+	+/-	+	+	↑	+	Unknown/+

worsened clinical manifestations of a preexisting infection or unmasking of a clinically silent infection [11].

Another condition in which antimicrobial treatment may trigger IRIS is Whipple's disease, a chronic infection due to *Tropheryma whipplei* that develops in immunologically susceptible individuals [12]. Here, the initial reduction in CD4⁺ cell counts and their reconstitution on treatment is more pronounced in those patients who developed IRIS than in those without IRIS [13]. Moreover, an imbalance between activated CD4⁺ T cells and regulatory T cells seem to play a crucial role in triggering the cytokine storm. Notably, *T. whipplei*-specific T-helper 1 reactivity remained suppressed before and after emergence of IRIS, thus indicating that flare-up of pathogen-specific immunoreactivity is not instrumental in the pathogenesis of IRIS. This implies that independent of the causal infectious agent, IRIS may possibly emerge in those carrying a specific immunological status and that the therapeutic approach may be the same. Therefore, efforts should be undertaken to identify the predisposing dysfunctional immune condition.

Multiple pathogens cause IRIS, which can manifest systemically or localize to the lung. The mechanisms involved in its immunopathogenesis are complex and not entirely understood [14]. The harmful effect of immune response to viral triggers on immunosuppressed patients who experience IRIS with immune recovery (followed by worsening various infections) has also been well described in the allogeneic HCT literature [15]. Respiratory viruses have been suggested to play a role in the pathogenesis of alloimmune-mediated lung syndromes [16]. It remains to be ascertained whether treatment of COVID-19 in susceptible immunocompromised hosts may trigger IRIS.

The immune dysregulation seen in CRS and sHLH/MAS has recently been described in some patients with severe COVID-19 and overlaps with IRIS (Figure 1 and Table 1); therefore, applying lessons learned from the cell therapy literature may provide important insights into severity classification and prognostic clues [17].

Biologic therapies and immunotherapy used to dampen hyperimmune responses

IL-6 inhibitors

Tocilizumab (ActemraTM) is a recombinant humanized monoclonal antibody directed against the IL-6 receptor. Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of

immunological responses. Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production.

IL-6 is a pleotropic cytokine with both anti- and pro-inflammatory effects. It is mainly produced by T cells and macrophages upon a tissue injury but also from skeletal muscle, smooth muscle in blood vessels, adipocytes and, notably, by lung epithelial cells [18]. It could be hypothesized that myalgias, microthrombi formation and higher complications in obese patients could be associated to IL-6 effects. Moreover, IL-6 crosses the blood–brain barrier and triggers the increase of body temperature through the release of prostaglandin E₂ (PGE₂).

Tocilizumab is indicated for adult patients with autoimmune disorders such as rheumatoid arthritis and was approved by the U.S. Food and Drug Administration (FDA) in 2017 for severe, life-threatening, CAR-T-cell–induced CRS in adults and children. The optimal dose and schedule of tocilizumab for treatment of CAR-T-cell–induced CRS is not known, but dosing instructions in tocilizumab labeling provide general recommendations for safe dosing. The FDA-recommended dose of tocilizumab in CAR-T induced CRS is 8 mg/kg intravenously (12 mg/kg for patients <30 kg body weight) alone or in combination with corticosteroids.

In a study of 40 hospitalized symptomatic COVID-19 patients, the median IL-6 was reported 27.1 pg/mL (range 0–430 pg/mL). The risk of respiratory failure for patients with IL-6 levels of ≥80 pg/ml was 92% and thus 22 times higher compared with patients with lower IL-6 levels. After reaching an IL-6 value of 80 pg/mL, the median time to mechanical ventilation was 1.5 days (range 0–4 days) [19] (Table 4). In contrast, some patients with Grade 4 CRS after CART-19 infusion, may have IL-6 levels greater than 600 pg/mL (120-fold increased from baseline) [20].

The rapid clinical stabilization frequently seen after systemic tocilizumab administration to CRS patients strongly implicates a cytokine array, including IL-8, IL-20, IL-21, IL-22 and dominated by IL-6, in the pathophysiology of the syndrome [9]. The median time from the onset of CRS to the first dose of tocilizumab has been reported to be 4 days (range, 0–18 days) [21]. Temperature often normalizes within a few hours after tocilizumab administration, whereas the other components of CRS take longer to resolve. In previous CAR-T clinical trials, patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if not more than 2 doses of tocilizumab were needed, and if no drugs other than tocilizumab and corticosteroids were used for treatment. Approximately 70% of patients achieve a response under this definition [21]. Tocilizumab has a half-life 11–14 days; therefore, if given early, it could dampen

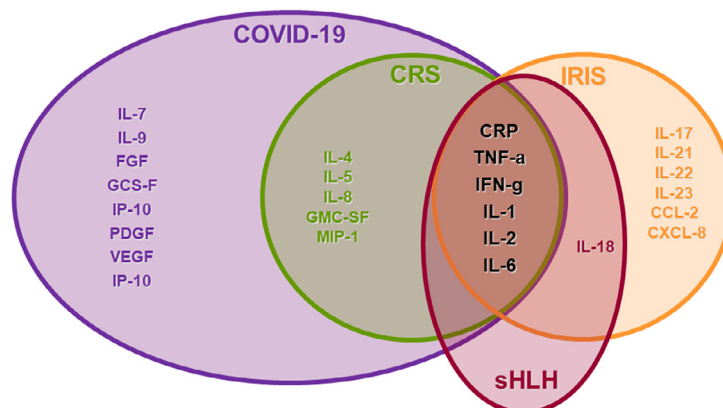


Figure 1. Overlapping cytokine profiles described in patients with COVID-19, CRS, sHLH and IRIS suggest pathophysiological similarities and potential for shared therapeutic interventions. CCL = chemokine ligand, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CRS = Cytokine release syndrome, CXCL = CXC chemokine ligand, FGF = fibroblast growth factor, G-CSF = granulocyte colony-stimulating factor, GMCSF = Granulocyte-macrophage colony-stimulating factor, IFN- γ = interferon γ , IL = interleukin, IP = induced protein, IRIS = Immune Reconstitution Inflammatory Syndrome, MCP = monocyte chemoattractant protein, MIP = macrophage inflammatory protein, PDGF = Platelet-derived growth factor, sHLH = Secondary hemophagocytic lymphohistiocytosis, TNF- α = tumor necrosis factor α , VEGF = vascular endothelial growth factor. References: Huang. Lancet 2020 (COVID-19); Brudno. Blood 2019 (CAR-T); Gopal. Eur Resp Review 2017 (IRIS); Schulert. Best Practice Rheum 2014 (sHLH). (Color version of figure is available online).

hyperimmune responses thought to be related to clinical decline in COVID-19 patients who progress to respiratory failure.

Given the similarities between CRS and COVID-19 hypercytokinemia and clinical symptoms, the clinical benefits and safety of tocilizumab is currently being systematically studied.

The efficacy of IL-6–IL-6R antagonists for the treatment of CRS as well as sHLH underscores the central role of IL-6 signaling in the pathophysiology of cytokine-driven hyperinflammatory syndromes [22]. Severe COVID-19 cases may benefit from IL-6 pathway inhibition given the associated CRS- and sHLH-like serum cytokine elevations [3].

Currently, tocilizumab is being investigated in an FDA-approved randomized, double-blind, placebo-controlled phase III clinical trial to evaluate its safety and efficacy when used with standard of care in hospitalized adult patients with severe COVID-19 and in a phase II study in Italy approved by the Italian Agency of Pharmaceutics.

Siltuximab (Sylvant™) is a human murine chimeric monoclonal antibody that binds IL-6 directly, in contrast to tocilizumab that binds to the IL-6 receptor. Siltuximab has a higher affinity for IL-6 than tocilizumab has for the IL-6R making it an attractive consideration in managing CRS. There is some concern that circulating IL-6 levels increase after administration of tocilizumab, contributing to an increased incidence of neurotoxicity [20,23]. This does not seem to be a concern with siltuximab, which is the rationale for its proposed benefit in tocilizumab-refractory cases, although no data are currently available on its efficacy. Siltuximab has not been sufficiently studied as a treatment for CRS and its use remains investigational; therefore, it should be considered only as second line agent in cases of COVID-19.

IL-1 inhibitor

Data from a phase 3 randomized controlled trial of anakinra (Kinere™) in sepsis, showed significant increase in survival in patients with hyperinflammation, without increased adverse events [24]. Currently, Swedish Orphan Biovitrum has an open-label, multicenter clinical trial evaluating the use of anakinra in combination with emapalumab at reducing hyperinflammation in severe COVID-19 patients. Patients in the anakinra arm, will receive anakinra intravenous (IV) infusion four times daily for 15 days (400 mg/day, divided in four daily doses).

It is important to note that IL-1 can be detected in the sera of mouse models of cytokine storm; however, correlation with the serum levels of IL-1 and disease severity has not been described for COVID-19 patients. The sensitivity and sensibility of currently available ELISA kits for human IL-1 are being validated. Gene expression and single-cell RNAseq data suggest that a signature related to NF- κ B pathway and possibly inflammasome activation might be present [25].

JAK-STAT inhibitors

Targeting inflammatory cytokine signaling via Janus kinase/signal transducers and activators of transcription (JAK-STAT) inhibition to treat CRS is being reported [26]. Baricitinib, fedratinib and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammatories that, as JAK-STAT signaling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon- γ) typically observed in people with COVID-19 [5].

BTK-inhibitors

Clinical trials examining the potential benefit for Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib (Imbruvica™) to protect

against lung pathology in patients with COVID-19 are being initiated. The clinical course of six patients who were receiving the drug for Waldenstrom's macroglobulinemia and became ill with COVID-19 was recently reported. The authors proposed that BTK-inhibition may provide protection against lung injury and even improve pulmonary function in hypoxic patients with COVID-19 [27].

Convalescent Plasma

Immunotherapy with neutralizing antibodies present in convalescent plasma proved to be safe and during the SARS, MERS and 2009 H1N1 influenza epidemics [28,29]. The feasibility of convalescent plasma transfusion to rescue severely ill patients with COVID-19 was explored in 10 patients in Wuhan, China. One dose (200 mL) of convalescent plasma was well tolerated, seemed to significantly improve clinical symptoms within 3 days and resulted in high-level neutralizing antibodies, leading to disappearance of viremia in 7 days. These results should be validated in larger cohorts, preferably with randomized trials [30].

Vaccination

Currently, there are no approved immunizations for COVID-19. A National Institutes of Health–sponsored phase 1 study is currently evaluating the experimental vaccine mRNA-1273 (Moderna, Inc., Cambridge, Ma, USA) in healthy subjects aged 18 to 55 years. This is a novel lipid nanoparticle-encapsulated mRNA vaccine that encodes for a prefusion stabilized form of the spike (S) protein of SARS-CoV-2. The primary objective of the study is to evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across three dosages (three different doses being tested, each given twice. E.g. (hypothetically) 50 mg on day 0, 50 mg on day 5; 100 mg on day 0, 100 mg on day 5; 500 mg on day 0, 500 mg on day 5) (<https://www.clinicaltrials.gov/ct2/show/NCT04283461>). Multiple other vaccination studies are currently under development.

Immunomodulation

MSCs

MSCs have immunomodulatory properties that make them potential therapeutic tools to repair tissue damage and dampen inflammation in immune-mediated disorders. Indeed, their action is displayed not only in all immune cells, but also in cell populations, such as epithelial cells, endothelial cells, fibroblasts, which take part in inflammatory cascades and are not targeted by other therapies. Moreover, MSCs are an attractive therapeutic option because they elicit no (or a weak) allogeneic immune responses when delivered to a non-identical, non-matched recipient and because they can easily be extracted from a variety of tissues including bone marrow, adipose and placental tissues including umbilical cord blood, and expanded in vitro as well as due to their high safety profile independent to the tissue source and clinical setting [31]. Although they show great promise in the treatment of many immune and inflammatory disorders, the large variability in manufactured cell products, donor cell quality, dosages, formulation as fresh or cryopreserved and differing administration routes have obscured their potential therapeutic benefit. To overcome these hurdles, a careful evaluation of appropriate cell sources, more scientific data and a better mechanistic understanding of immunosuppression of MSCs is needed [32]. The START clinical phase II study has the highest number of MSC-treated patients suffering from (non-COVID) acute respiratory distress syndrome (ARDS; n = 40), that is, it showed that a single dose of allogeneic bone marrow-derived MSCs did not cause short- or long-term hemodynamic or respiratory adverse events

over a 60-day follow-up period. However, no significant improvement in the mortality rate related to ARDS was observed. This may be due to differences in the disease severity within the study populations as well as low MSC viability, ranging from only 35 to 80% [33].

During the SARS-CoV-2 outbreak in China, several clinical studies were open and are still ongoing, with one already published: a single-center open-label pilot investigation from the YouAn Hospital in Beijing administered BM-derived MSCs to seven patients with COVID-19 pneumonia with differing degrees of severity including one patient with critically severe disease requiring ICU care [27]. The MSCs were given as a single intravenous administration at a dose of 10^6 cells/kg body weight in 100 mL of saline at various times after initial symptomatic presentation. The seven patients were categorized as critically severe ($n = 1$), severe ($n = 4$) and common type ($n = 2$). Three additional patients classified as severe received placebo for comparison. Patients were followed for 14 days after MSC or placebo administration and a range of safety and efficacy endpoints were assessed. No infusion toxicities or severe attributable adverse events were observed and patients, including the one categorized as critically severe, apparently demonstrated clinical improvements within 2 to 4 days after MSC administration. However, although detailed clinical information as well as information on levels of circulating inflammatory mediators and of inflammatory cell populations were presented, there is a lack of corresponding information for the other six patients or for the three placebo patients. As such, more information regarding inclusion and exclusion criteria, timing of MSC administration relative to disease onset, comorbidities, the clinical course of each patient and a comprehensive evaluation of inflammatory mediators for both treated and placebo patients are required to better determine the potential efficacy of MSC and their mechanisms of action in this setting [35].

In parallel with studies evaluating the potency of MSC for the treatment COVID-19 in China, there are now several centers globally both in the academic and industry-sponsored settings evaluating MSC for this disease. Results from these studies should be forthcoming soon.

Virus-specific T cells

Virus-specific T cells (VSTs) have been successfully generated against several viruses including cytomegalovirus (CMV), Epstein-Barr virus, adenovirus, [51–55] human herpes virus (HHV)-6, BK polyomavirus (BK), [56] parainfluenza virus, [65] Zika virus, [57] mycobacteria, [58] norovirus, [59] herpes simplex virus (HSV-1), [60] HIV [61] and others. Of these, T cells targeting CMV, Epstein-Barr virus, adenovirus, HHV6, BK virus, parainfluenza and HIV [62] have been tested in patients, with a strong safety profile and many demonstrating promising clinical responses worthy of further clinical evaluation [63]. To broaden access to these cell therapies, several investigators and companies have extended this technology to off-the-shelf allogeneic T cells, where the patient and product are partially human leukocyte antigen (HLA) matched. This could present an appealing opportunity for SARS-CoV2-specific T cells. A bank of SARS-CoV2-specific T cells could be created from a diverse range of donors covering diverse HLA alleles, and a personalized product would be selected for each patient based on the degree of HLA match [64]. This would allow for rapid shipment and treatment of patients, albeit in hospitals with existing cell therapy expertise and resources.

Natural killer cells

Natural killer (NK) cells are lymphocytes that recognize targets via the absence of ligands such as HLA and a complex array of activating and inhibitory receptors. Unlike T cells, NK cells do not

rely on peptides presented in the presence of HLA, which makes NK cells an ideal cell therapy for allogeneic, off-the-shelf use. A role for NK cells in the prevention of relapse after HCT has been postulated previously, and recently, CAR NK cells have shown promise in a study of patients with CD19-positive non-Hodgkin's lymphoma or chronic lymphocytic leukemia. Recently, the FDA granted investigators from the biotechnology company Celularity clearance to test whether cryopreserved, allogeneic NK cells derived from placental hematopoietic stem cells are capable of lysing virus-infected cells and control the resulting immune response. However, aside from clinical data of the NK cell product CYNK-001, there is limited public information about the efficacy of CYNK-001 or other NK cells against COVID-19 [36–38].

Extravascular vesicles

Extravascular vesicles (EVs) are a heterogeneous group of cell-derived membranous structures, including exosomes and microvesicles, which are involved in intercellular communication, thus important for multiple physiological and pathological processes [39]. The broad and increasing interest in EVs has opened the opportunity to use exosomes and microvesicles both as biomarkers to follow the progression of various pathological states, as well as potential therapeutic modalities. In particular, MSC-derived EVs have been shown in a range of preclinical studies, including those of acute lung injury, to be as effective as the parent cells themselves [40]. However, there are several issues including but not limited to source, isolation and purification approaches, manufacturing consistency and potency that are in evolution and yet no clinical investigations in patients with ARDS [41]. As such, it is likely premature to consider use of EVs for COVID-19 respiratory disease.

Corticosteroids

Evidence in patients with SARS and MERS suggests that administration of corticosteroids did not influence mortality but rather delayed viral clearance [42]. Moreover, current interim guidance from the World Health Organization on clinical management of severe acute respiratory infection when novel coronavirus infection is suspected advises against the use of corticosteroids unless indicated for another reason [43]. However, in hyperinflammatory states, immunosuppression is likely to be beneficial (Mehta. *Lancet* 2020) and may be worth trying for critically ill COVID-19 patients. Further well-designed clinical trials are urgently needed to evaluate the safety and efficacy of steroid therapy in COVID-19.

Drugs with antiviral activity

The combination of two antiviral molecules (lopinavir, a human immunodeficiency virus type 1 aspartate protease inhibitor, plus ritonavir, an inhibitor of the cytochrome P450 to increase its plasma half-life) has been tried for COVID-19. However, convincing data are lacking as recently demonstrated, the association of lopinavir-ritonavir has proved unfruitful compared with standard of care in an adult cohort of hospitalized patients with severe SARS-CoV-2 pneumonia [44]. Therefore, further antiviral agents have been proposed.

Hydroxychloroquine and chloroquine are drugs that interfere with digestive vacuole function within sensitive malarial parasites by increasing the pH and inhibiting lysosomal degradation of hemoglobin; inhibit locomotion of neutrophils and chemotaxis of eosinophils and; impair complement-dependent antigen-antibody reactions. Chloroquine has been used for malaria treatment and chemoprophylaxis and hydroxychloroquine is used for treatment of several autoimmune conditions including rheumatoid arthritis. Both drugs have *in vitro* activity against coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2 [45]. On the basis

Table 3
American Society for Transplantation and Cellular Therapy CAR-T-related CRS consensus grading.

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever ^a	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or ^b Hypoxia	None	Requiring low-flow nasal cannula ^c or blow-by	Requiring high-flow nasal cannula ^c , face-mask, nonrebreather mask, or venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

BiPAP; bilevel positive airway pressure; CPAP, Continuous positive airway pressure.

^a Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

^b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

^c Low-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L}/\text{min}$. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $>6\text{L}/\text{min}$.

Table 4
COVID-19 Laboratory Parameters (adapted from Herold et al., 2020) [19].

Laboratory parameters	Evaluable	Median (range)	Mechanical ventilation		P value
			No (n = 27)	Yes (n = 13)	
Lymphocyte count (%)	36	19 (4–45)	21 (4–45)	15 (6–26)	0.050
CRP (mg/dl)	40	2.8 (0–31.5)	1.7 (0–31.5)	7.8 (1.6–17.1)	0.0019
Bilirubin (mg/dl)	36	0.5 (0.2–1.9)	0.5 (0.2–1.2)	0.5 (0.4–1.9)	0.93
WBC (G/l)	40	5.295 (2.12–308)	4.75 (2.12–12.5)	6.64 (4.99–308)	0.0014
LDH (U/l)	38	292 (182–1078)	281 (182–619)	346 (252–1078)	0.0026
PCT (mg/ml)	37	0 (0–5)	0 (0–0.6)	0.1 (0–5)	0.011
IL6 (pg/ml)	37	27.1 (0–430)	19.6 (0–76.5)	121 (19.2–430)	0.000012
Platelet count (G/ml)	40	165 (88–440)	186 (88–334)	160 (1–440)	0.59
Troponin T (ng/ml)	34	0 (0–0.032)	0 (0–0.022)	0 (0–0.032)	0.018
Creatinine (mg/dl)	40	0.9 (0.4–2.1)	0.9 (0.4–1.3)	1.0 (0.9–2.1)	0.00034
D-Dimer	30	0.7 (0–2.9)	0.6 (0–2.2)	1.1 (0.6–2.9)	0.028
Ferritin (ng/ml)	27	644 (64–2153)	606 (64–1748)	810 (431–2153)	0.16

CRP, C-reactive protein; LDH = lactate dehydrogenase; PCT = Procalcitonin; WBC, white blood cell count.

of limited *in vitro* and anecdotal data, chloroquine or hydroxychloroquine administered either with or without azithromycin (a macrolide with anti-inflammatory properties) have been recommended for treatment of hospitalized COVID-19 patients in several countries. However, due to the potential for serious adverse effects, especially when combined with other drugs, caution is advised until peer-reviewed data are available.

Remdesivir is an investigational antiviral which blocks viral replication by inhibiting RNA synthesis [46]. It has broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has *in vitro* activity against SARS-CoV-2 and *in vitro* and *in vivo* activity against related beta coronaviruses [45]. Currently, it can be obtained for IV use in hospitalized patients with COVID-19 through an National Institutes of Health-sponsored double-blind placebo-controlled trial (<https://clinicaltrials.gov/ct2/show/NCT04280705>), two phase 3 randomized open-label trials (<https://clinicaltrials.gov/ct2/show/NCT04292899> and <https://clinicaltrials.gov/ct2/show/NCT04292730>) or on an uncontrolled compassionate use basis. In a cohort of patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Due to study limitations such as cohort size and single arm design, efficacy will require ongoing randomized, placebo-controlled trials [47].

Other potentially interesting treatments currently being studied include the use of emapalumab (anti-interferon- γ monoclonal antibody Sobi-IMMUNO-101 study) and the antiparasitic ivermectin [48].

To date, more than 600 worldwide studies and clinical trials investigating COVID-19 are underway. (Appendix 1: COVID-19 Clinical Trials). Rigorous premarketing evaluation of drugs' safety and effectiveness in randomized, controlled trials remains the primary

tool for protecting the public from drugs that are ineffective, unsafe or both [49].

Conclusion

In conclusion, SARS-CoV-2 is a novel betacoronavirus currently causing a pandemic of unprecedented modern proportions. COVID-19 ranges from mild viral illness in most hosts to life-threatening disease in a subset of patients who develop hyperimmune inflammatory responses. Further studies aimed at unraveling the immune response in lung and peripheral blood will aid in understanding the risk of developing ARDS is based on preexisting conditions and not the virus itself.

In the absence of FDA- and European Medicines Agency-approved treatments for COVID-19, management currently relies on supportive care. Ongoing reports of clinical and laboratory features of COVID-19 show significant overlap with hyperinflammatory conditions such as CRS, sHLH and IRIS. Early recognition and treatment of hosts who display the hallmarks of CRS, sHLH and SIRS is of utmost importance to reduce morbidity and mortality. A number of therapeutics approved for other indications as well as investigational agents are currently being evaluated in several hundred clinical trials globally. Experiences derived from therapeutics employed for the treatment of complications secondary to immunotherapies, such as CAR-T, bispecific monoclonal antibodies and HCT, may provide a safe framework for the classification and early intervention of patients who are at the highest risk of dying from COVID-19-related complications. Despite the urgency of the pandemic, extreme caution must be exercised to avoid the use of unproven therapeutics based on

limited data from poorly conducted clinical trials and/or observational data [34,50]. Well-designed and appropriately conducted randomized controlled trials are therefore essential to find a definite answer.

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Declaration of Competing Interest

PJH: Stock, other ownership interests, and serves on the board of directors of Mana Therapeutics. Intellectual property related to virus-specific T cells. BL: Stock and other ownership interests in Tmunity Therapeutics; honoraria: Novartis, Terumo, AstraZeneca; consulting or advisory role: Brammer Bio/ThermoFisher Viral Vector services, Avectas, Immuneel, Ori Biotech and Vycellix. VB: BioNTech AG, patent and research collaboration; Ganymed Pharmaceuticals AG, research collaboration; Xios Therapeutics, Scientific Advisory Board; Codiak BioSciences, scientific advisory board; Incyte Corporation, research collaboration. CMB: Stock, Scientific Advisory Board, other ownership interests in Mana Therapeutics. Stock, Cogen Immune Medicine and Neximmune; stock, board of directors, Cabaletta Bio; stock, Scientific Advisory Board, Catamaran Bio; Intellectual property related to virus-specific T cells and NK cells. JJB: DMC member/chair (consulting); advanced clinical consulting: AvroBio, Takeda, Omeros, Bluebird Bio, BlueRock, Race Oncology; grants: Sanofi (unrestricted grant for clinical trial). The other authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: MC, JJB, PH. Analysis and interpretation of data: MC, PH, JJB, BL, RC, PR, VB, DW, CB. Drafting or revising the manuscript: MC, PH, JJB, BL, RC, PR, VB, DW, CB. All authors have approved the final article.

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