Editorial

The Rheumatologist's Role in COVID-19

The novel coronavirus (severe acute respiratory syndrome; SARS-CoV-2) pandemic has spread rapidly throughout the planet. It is believed to have originated in the Wuhan province of China, but this highly contagious respiratory virus has spread to over 140 countries on 6 continents as of mid-March 2020, according to the World Health Organization. Worldwide, there have been over 164,000 cases identified and over 6500 deaths attributed to the viral infection. As of mid-March 2020, there are over 3700 confirmed cases and 68 deaths ascribed to the coronavirus disease 2019 (COVID-19; the disease caused by SARS-CoV-2) in the United States (www.livescience.com/coronavirus-updates-united-states.html). These numbers will only continue to grow globally. Based primarily on data out of China, about 80% of those infected with SARS-CoV-2 experience a relatively mild "cold," as is seen with more common coronavirus infections. However, 20% of those infected require hospitalization, with 5–15% overall necessitating intensive care[1]. As the true denominator of those infected is not yet known, it remains unclear what the overall mortality rate is associated with COVID-19, but estimates range between 1% and 4%[2]. Although the mortality rate is lower than that reported for previous coronavirus epidemics such as SARS and MERS (Middle East respiratory syndrome), the much larger absolute number of infected individuals with SARS-CoV-2 will result in substantially more total deaths worldwide.

Those at highest risk of dying from COVID-19 are elderly (> 60 yrs and increasing with age), those with immunodeficiencies, and those with underlying chronic medical conditions (e.g., diabetes, heart disease). Although children tend to experience only mild symptoms, younger previously healthy adults have also succumbed to COVID-19. Once hospitalized, for some patients, death can occur within a few days, many with adult respiratory distress syndrome, and some with multiorgan dysfunction syndrome[3]. In those critically ill patients, there are both clinical signs and symptoms, as well as laboratory abnormalities, that suggest a cytokine storm syndrome (CSS) is occurring in response to the viral infection. Specifically, COVID-19 patients with CSS may have high fevers, confusion, and coagulopathy (Table 1)[3]. In addition, reports out of China have detailed the following commonly seen CSS laboratory abnormalities in hospitalized patients with COVID-19: elevated liver enzymes, C-reactive protein, ferritin, soluble interleukin (IL)-2 receptor α-chain, D-dimers, coagulation times, and lactate dehydrogenase; with lower platelet and lymphocyte counts (Table 1)[3,4,5]. Physicians thus need to be aware of the possibility of CSS occurring in their hospitalized patients with COVID-19[6]. Because rheumatologists are aware of CSS/macrophage activation syndrome (MAS) among their own patient populations (e.g., adult-onset Still disease, systemic juvenile idiopathic arthritis, systemic lupus erythematosus), they can help to champion the screening for, and diagnosis of, CSS among hospitalized patients with COVID-19.

There is no perfect set of diagnostic criteria available for diagnosis of CSS, particularly in the setting of COVID-19 (new territory), but currently available CSS criteria [e.g., HScore, hemophagocytic lymphohistiocytosis (HLH)-04, ferritin to erythrocyte sedimentation rate ratio; Table 1) can certainly guide clinicians toward the clinical diagnosis[7,8,9]. As a simple, cheap, readily available, and fast screen, we propose that every hospitalized patient with COVID-19 is deserving of a serum ferritin value[7,10]. A notably elevated ferritin value (e.g., > 700 ng/ml) should alert clinicians to additional diagnostic investigation so that therapeutic approaches can be considered without significant delay. As one might expect, the earlier the institution of treatment for CSS, the better the outcomes[11].

The ideal treatment for COVID-19–induced CSS is unknown. It is hoped that the institution of randomized clinical trials will address this issue. Until then, clinicians should exercise standard-of-care therapy for viral-triggered CSS. Rheumatologists, hematooncologists, intensivists, infectious diseases experts, and other relevant healthcare providers should develop a uniform approach to care for COVID-19 patients with CSS, with the implicit understanding that deviations from this approach may be necessary on an individual case basis[12]. At this time, there is no uniformly accepted treatment algorithm for patients with CSS. The good and the bad news is that there is now a variety of therapeutic options available to treat CSS, but the ideal treatment (or combination of treatments) is unclear[13]. We can, however, learn from experience.

CSS can be the result of rare familial homozygous genetic defects in perforin pathway proteins. Infants with familial HLH (1 in 50,000 live births) will die from the CSS unless the CSS is aggressively treated, followed by stem cell transplantation. The standard therapy for these newborns is

Table 1. Clinical and laboratory features of cytokine storm syndrome reported in COVID-19 patients and their relationship to cytokine storm syndrome criteria.

HLH-04 Criteria[9]	HScore[8]	Ferritin:ESR Ratio[7]	COVID-19 Features[3,4,5,24,25]
Fever	Fever		Yes
Splenomegaly	Splenomegaly		Unknown
	Hepatomegaly		Unknown
Anemia	Anemia		Yes
Thrombocytopenia	Thrombocytopenia		Yes
Neutropenia	Neutropenia		Yes
Hypertriglyceridemia	Hypertriglyceridemia		Unknown
Hypofibrinogenemia	Hypofibrinogenemia		Yes
Hemophagocytosis	Hemophagocytosis		Unknown
Low NK cell activity			Unknown
Hyperferritinemia	Hyperferritinemia	Hyperferritinemia	Yes
Elevated soluble CD25	Elevated soluble CD25		Yes
	Elevated serum GGT		Unknown, but AST and ALT elevated
	Underlying immunosuppression		Some with HIV infection
		Falling ESR	Unknown

COVID-19: coronavirus disease 2019; HLH: hemophagocytic lymphohistiocytosis; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HIV: human immunodeficiency virus; NK: natural killer; GGT: gamma-glutamyl transferase.

an etoposide-based chemotherapeutic regimen with substantial overall morbidity and mortality[9]. More recently, a cytokine-directed approach to familial CSS has been approved by the US Food and Drug Administration[14]. Specifically, anti–interferon-γ (IFN-γ) was beneficial in treating refractory familial HLH, and clinical trials are ongoing to study targeting of IFN-γ in older children and adults with later-onset CSS.

Prior to the use of anti-IFN-γ treatment for CSS, other effective cytokine-targeted approaches were reported. Perhaps the best-studied is recombinant human IL-1 receptor antagonist (rhIL-1Ra, anakinra), which was recently reported to provide 73% survival among a cohort (n = 44) of rheumatic, infectious, and oncologic patients[11]. In a retrospective analysis of a prospective randomized and blinded placebo-controlled clinical trial, rhIL-1Ra also nearly doubled survival of sepsis patients with features of CSS[15]. Currently, rhIL-1Ra is being studied in a randomized and blinded placebo-controlled trial to treat children and adults with CSS (ClinicalTrials.gov: NCT02780583).

In addition to IL-1 and IFN-γ blockade, disruption of IL-6 signaling with anti–IL-6 receptor monoclonal antibody, tocilizumab, has been shown effective in treating cytokine release syndrome, a common complication of CAR-T cell therapy used for treating refractory leukemia[16]. Because IL-6 levels can be easily measured in the blood, IL-6 levels have been studied and reported to be elevated in hospitalized patients with COVID-19[4]. It has been reported that the anti–IL-6R antibody tocilizumab has been beneficial in treating Chinese COVID-19 patients with CSS[17]. In addition, small molecule inhibitors of Janus kinases (JAK), such as the JAK1/2 inhibitor, ruxolitinib, are capable of blocking signaling downstream of IL-6, IFN-γ, and other cytokines[18,19]. Thus there may be a variety of targeted cytokine inhibitors available that may benefit patients with COVID-19–induced CSS (Table 2).

Table 2. Targeted approaches to blocking inflammatory cytokines in cytokine storm syndrome.

Inflammatory Cytokine	Therapeutic	Reference
IL-1	Anakinra	11
IL-6	Tocilizumab	16
IL-18	Tadekinig alpha	26
IFN-γ	Emapalumab	27
IL-6, IFN-γ, others	Ruxolitinib	28
TNF	Infliximab	29

IL: interleukin; IFN: interferon; TNF: tumor necrosis factor.

Similar to deadly flu outbreaks, such as the 2009 H1N1 influenza, SARS-CoV-2 appears to trigger a cytokine storm in a subset of individuals. Interestingly, in a cohort of patients who died from the 2009 H1N1 influenza, 36% harbored 1 or 2 different heterozygous familial HLH gene mutations critical to the perforin pathway of lymphocyte-mediated target cell lysis[20]. The tissue pathology from these patients also demonstrated extensive hemophagocytosis throughout, also consistent with the CSS of HLH[21]. Perhaps the 20% of patients requiring hospitalization for COVID-19 share similar genetic risk factors. Without knowing the genetic risk factors at present, treating physicians need to treat their patients based on the severity and degree of manifestations presented. If CSS is suspected (e.g., high serum ferritin) in a febrile hospitalized patient with COVID-19, then early institution of CSS-directed therapy will likely save lives.

Among the ever-growing array of cytokines to target for CSS are IL-1, IL-6, IL-18, IFN-γ, and even tumor necrosis factor (Table 2). Because IL-6 levels are high, and blocking IL-6 is effective for treating cytokine release syndrome, and anti–IL-6R antibody has been deployed in treating Chinese patients with COVID-19, it seems like a reasonable approach. In addition, IL-1 blockade with rhIL-1Ra (anakinra) has proven efficacious in a wide array of medical conditions (such as herpes virus family infections) associated with CSS/MAS, and anakinra has a variety of agreeable properties[22]. Anakinra can be given intravenously or subcutaneously; it is a recombinant human protein with a well-studied favorable safety profile; it has a short half-life of about 4 h and a large therapeutic window (1–48 mg/kg/day have been tested). When anakinra is effective for CSS, it works within 48–72 h[23].

Until results from clinical trials of biologic anticytokine agents used to treat COVID-19 CSS are available, physicians will need to rely on a unified approach to treating these desperately ill individuals. As this coronavirus pandemic broadens, rheumatologists are well-positioned to assist in managing CSS associated with this illness. Rheumatologists have a strong background in understanding the immune system, are familiar with CSS such as MAS because many of their patients develop it, and are most practiced with using cytokine-targeting therapy (e.g., IL-1 blockade, IL-6 blockade). Rheumatologists can assist and work together with their colleagues in other subspecialties to diagnose and to treat those patients with COVID-19 who develop CSS. This cooperative effort should help reduce mortality during these trying times.

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First Release April 15 2020; J Rheumatol 2020;47:639-42; doi:10.3899/jrheum.200334