Immune modulation in COVID-19: Strategic considerations for personalized therapeutic intervention

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Key words
COVID-19, immunoparalysis, cytokine storm, immune modulation, inflammation

Summary
There is unlikely to be a “one size fits all” approach to immunodulation in patients with COVID-19. Clinical trials of immunomodulators in this setting should include prospective immunophenotyping and should adapt to the dynamic nature of the host immune response.

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Abstract

We are learning that the host response to SARS-CoV-2 infection is complex and highly dynamic. Effective initial host defense in the lung is associated with mild symptoms and disease resolution. Viral evasion of the immune response can lead to refractory alveolar damage, ineffective lung repair mechanisms, and systemic inflammation with associated organ dysfunction. The immune response in these patients is highly variable and can include moderate to severe systemic inflammation and/or marked systemic immune suppression. There is unlikely to be a “one size fits all” approach to immunomodulation in patients with COVID-19. We believe that a personalized, immunophenotype-driven approach to immunomodulation that may include anti-cytokine therapy in carefully selected patients and immunostimulatory therapies in others is the shortest path to success in the study and treatment of patients with critical illness due to COVID-19.
Introduction

A vital component of our understanding of the pathogenesis of coronavirus disease 2019 (COVID-19) involves deconvoluting the complex spectrum of immune responses in COVID-19 patients. Despite the still emerging nature of the data, many early reports have enabled some characterization of the clinical course of this disease and associated immunological response against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Based on these reports, there seem to be three basic phases during the course of COVID-19 infection: the first being a largely asymptomatic incubation period, followed by symptom onset in the second phase that is non-specific and non-severe, with a subset of patients progressing to a third phase with severe lung disease, often with accompanying extra-pulmonary organ dysfunction [1-4]. While most patients promptly recover, many have poor clinical outcomes including prolonged ARDS and/or death. Concurrent with the pathophysiology of COVID-19 infection, the immune responses in these patients may be categorized into phases: an early local innate immune response that is critical for the host in providing anti-viral defense in the lung, and a later phase which results in severe local and systemic immune responses that contribute to morbidity and mortality [5].

A global race is on in search for a novel or repurposed antiviral agent to treat the infected and, ideally, decrease viral shedding and transmission. Concurrently much interest exists in controlling the hyperinflammatory state elicited by the infection. The inflammatory response in COVID-19 has been likened to conditions including classical acute respiratory distress syndrome (ARDS), macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH), or simply “cytokine storm” [6]. It is likely that none of these syndromes precisely fit all COVID-19 patients, lending urgency to the development of personalized-medicine approaches to the diagnosis and management of the inflammatory effects of this complex and novel disease above and beyond supportive care. Defining the biological processes in the various stages of COVID-19 at a granular level is critical to identifying targets for drug development and, in the absence of proven effective
therapies, informing empiric treatment decisions. It is also essential to look back over the history of treating deadly conditions like ARDS and sepsis in an effort to avoid pitfalls that our predecessors discovered decades ago.

Here, we summarize what is known and unknown about the immunobiology SARV-CoV-2 infection (Figure 1) and highlight the importance of following the science, past and present, in an effort to provide a balanced viewpoint on the development of therapeutic strategies for those affected with severe COVID-19.

Early Inflammatory Process

The ACE2-expressing cells act as target cells for SARS-CoV-2 infection [7]. In the lung, virus can infect and impair the respiratory tract mucosal epithelium, alveolar epithelium, bronchial mucosal epithelium and endothelial cells [8]. Importantly, the high expression of ACE2 in alveolar type II cells in the lung likely makes this cell type more susceptible to SARS-CoV-2 infection. Infection of alveolar type II cells may be an underpinning of COVID-19 pathogenesis as these cells are known to perform many critical functions that include production of pulmonary surfactant, airway epithelial barrier stabilization, and airway regeneration in response to injury. They also play a role in immune defense via secretion of cytokines in response to alveolar damage and pathogens in order to signal the recruitment and activation of macrophages and other immune cells in defense of the alveolus [9].

Given the high prevalence of mildly symptomatic patients, this early, local immune response can often successfully contain the initial viral infection and re-establish the homeostatic environment in the respiratory tract. Successful control of viral infections often depends on the initiation of types I-III interferon (IFN) responses and their downstream signaling events. These signaling events eventually also translate into an effective adaptive immune response [10]. Also critical during this phase may be the collaboration of transforming growing factor beta (TGF-β) with IL-6 to induce the differentiation of naïve CD4 into Th17 cells [11]. IL-6 is known to further synergize with IL-7 and IL-15 to induce the differentiation and cytolytic capacity of the CD8 T cells [12].
Immune Escape Process

The IFN response can often be suppressed or delayed in infections caused by viruses such as SARS-CoV, MERS-CoV, as well as influenza virus, with impairment of the IFN response correlating with greater disease severity [13, 14]. Although speculative, members of the Betacoronavirus family such as SARS-CoV, MERS-CoV and SARS-CoV-2 may have similarity in their mechanism of innate immune evasion. Recent studies have shown that the replication of SARS-CoV-2 in alveolar cells can result in a suppressed magnitude of antiviral response, with inhibition of IFN-I and IFN-III responses in both a human lung alveolar carcinoma cell line and in vivo in ferrets [15]. In addition, inoculation of SARS-CoV-2 onto ex vivo human lung tissue explants resulted in productive infection while inducing lower expression of IFNs and pro-inflammatory cytokines/chemokines, suggesting that SARS-CoV-2 is able to evade innate immune detection or suppress the downstream response [16]. Suppression of the innate immune response in the early phase would allow the SARS-CoV-2 to replicate unchecked in the respiratory tract, achieving high viral load and eventually contributing to its efficient person-to-person transmission before onset of severe clinical symptoms [17]. Indeed, this notion is supported by the high prevalence of radiological changes in CT scans of the lungs of COVID-19 patients, even in the early stages of illness. Evidence of adaptive immune dysfunction comes from autopsy reports of COVID-19 patients demonstrating low numbers of CD8 positive T lymphocytes infiltrating lung tissue [18]. There have also been clinical reports of decreased immune cell populations including CD4, CD8, and NK cells in peripheral blood [19]. Additionally, the NK cells and cytotoxic lymphocytes appeared to be exhausted with a reduced ability to produce CD107a, IFN-γ, IL-2, granzyme B, and TNF-α [20]. The T cells from COVID-19 patients also have significantly higher expression of the inhibitory molecule PD-1 compared to healthy controls. These increases in PD-1 and Tim-3 expression on T cells were reported as patients progressed from mildly symptomatic to severe stage, further indicative of T cell exhaustion.
Coronaviruses can also impair host defense through their effects on the Th1 cytokine GM-CSF. In addition to promoting the production of myeloid-lineage leukocytes in the bone marrow, GM-CSF is essential for the development and functional maturation of alveolar macrophages [21-23]. Alveolar macrophages are the sentinels of innate immune system against respiratory pathogens. They act via secretion of oxygen metabolites, anti-microbial proteases, and by recruiting activated neutrophils into alveolar spaces. They can also aid in resolving inflammation after the infectious challenge is resolved by restoring surfactant homeostasis and orchestrating epithelial proliferation and barrier repair [24]. Lung epithelial cells transfected with the SARS-CoV protease 3CLPro were shown to have decreased GM-CSF mRNA and protein expression suggesting that SARS-CoV may promote alveolar injury through the suppression of GM-CSF [25]. Whether this represent a mechanism of SARS-CoV-2-mediated immune suppression remains to be investigated.

Subsequent Inflammatory Process
Severe suppression of the host immune response is paradoxically associated with increased levels of cytokines in the systemic circulation in COVID-19 pneumonia patients [26, 27]. Severe lung damage due to unchecked viral replication can cause breakdown of epithelial barrier function leading to diffuse alveolar damage with increased microvascular permeability. There is leakage of pro-inflammatory cytokines such as IL-6, IL-8, IL-1β from parenchymal lung tissue into the systemic circulation and a concurrent recruitment of circulating immune cells into the lung. A counter-regulatory response is activated simultaneously, resulting in increased local and systemic levels of suppressive cytokines such as IL-10 and TGFβ [28]. This concurrent systemic elevation of both pro- and anti-inflammatory cytokines levels is frequently referred to as “cytokine storm”, the pro-inflammatory arm of which can result in malperfusion and worsening pulmonary and extrapulmonary organ function while its anti-inflammatory arm can result in severe suppression of circulating leukocyte function, or “immunoparalysis” [29]. The local pro-inflammatory milieu in the lung can overwhelm homeostatic tissue repair functions leading to irreversible tissue damage and
depletion of alveolar macrophages [30]. During this process activated fibroblasts can deposit excess collagen which further impairs pulmonary gas exchange. Epithelial cell death may also expose the basement membrane to secondary microbial pathogens offering them access to the systemic circulation [31]. Loss of alveolar macrophages can therefore represent a potential chief contributor to refractory respiratory failure in COVID-19 patients, with almost complete depletion of these cells reported in severely infected patients [32].

A Cautionary Tale of Immunomodulation

Most forms of acute critical illness have, at their roots, an initial pro-inflammatory insult, with sepsis and ARDS being the classic examples of disorders whose predominant pathophysiologic effects are due to an exaggerated host response. The use of anti-inflammatory drugs including prostaglandin E1 and ketoconazole (a thromboxane inhibitor) failed to improve ARDS outcomes in adults [33]. The use of corticosteroids in ARDS remains highly controversial with some studies showing improvement in outcomes following prolonged treatment with low-dose glucocorticoids [34]. The evidence was not, however, strong enough to merit inclusion in current pediatric or adult ARDS treatment guidelines [35-37]. A recent announcement from the RECOVERY trial group indicated that low-dose dexamethasone may improve outcomes in adults with COVID-19, though those data have yet to be peer-reviewed. Conversely, the use of GM-CSF in adults with ARDS, while safe, has not been associated with improved clinical outcomes [38]. None of these trials used a priori immune phenotyping to identify subjects who would be most likely to benefit from these interventions.

The 1980s and 1990s saw profusion of clinical trials in septic adults that targeted reduction of the pro-inflammatory response through removal or blockade of specific inflammatory mediators. Treatments that were evaluated included those aimed at reducing or removing endotoxin, TNFα, IL-1β, bradykinin, and others [39]. These therapies, along with high-dose glucocorticoids, were nearly all failures in phase III clinical trials, with some demonstrating increased mortality. Over the next two
decades, the field of immunomodulation in critical illness pivoted to focus more on the immunosuppressive phase of the host response, as we learned that critical illness-induced innate and adaptive immune suppression often occurs simultaneously with cytokine storm.

Immunoparalysis, with reduced antigen presentation capacity, impaired cytokine production capacity, and lymphopenia, has been strongly associated with adverse outcomes from critical illness including nosocomial infection, prolonged organ failure, and death [40]. There are now clinical trials being performed that target stimulation of immune function in selected critically ill patients with therapies such as recombinant GM-CSF (NCT03769844, NCT00252915), IFNγ (NCT03332225), and antibodies against PD-1 pathway members (NCT03332225). To be sure, there are several examples where specific anti-cytokine therapies have been shown to be beneficial, including anakinra for the treatment of macrophage activation syndrome and tocilizumab for the treatment of CAR-T cell therapy-induced cytokine release syndrome (CRS). These therapies, however, have specific biologic plausibility (e.g. inflammasome dysregulation in MAS) or particularly severe elevations in systemic cytokine levels [41]. For example, the serum levels of IL-6 seen in severe CAR-T cell therapy-induced CRS are in the many thousands of pg/ml, one or more orders of magnitude higher than those seen in most reports of severe COVID-19 disease to date [42]. The conflict inherent in the field’s current approach to immunodulation in adults hospitalized with COVID-19 is perhaps best exemplified by the fact there is at least one ongoing clinical trial which uses recombinant GM-CSF therapy (NCT04326920) while another active trial promotes GM-CSF blockade (NCT04341116) in a similar population.

There is unlikely to be a “one size fits all” approach that can be taken with regard to immunodulation in patient with COVID-19. A recent immune monitoring study in COVID-19+ adults showed a high degree of heterogeneity of immune phenotypes within the cohort [19]. Profound depletion of CD4+ lymphocytes and NK cells was common, as was marked reduction in monocyte antigen presenting capacity as measured by HLA-DR expression. MAS, with marked hyperferritinemia, occurred only in
a minority of subjects, as did severe elevations in systemic IL-6 levels. Immunomodulatory therapies that are, in our view, likely to be successful in patients with COVID-19 are those that are tailored to the patient’s immunophenotype in real time. Further suppression of the immune response has the potential to enhance the risk of bacterial and viral infections, promote the development of opportunistic infections, and potentiate the reactivation of latent viruses. It is also important to acknowledge that cytokine levels in peripheral blood do not necessarily reflect systemic leukocyte function or cytokine profiles at the actual site of infection in lung, and may peak after the nadir of respiratory function [43].

While nonpharmaceutical interventions such as physical distancing have played a key role in the management of the COVID-19 pandemic across the globe, additional approaches are needed to combat this virus in the longer term. These include accelerated vaccine development, effective antiviral medications, and targeted immunomodulatory approaches in the right patient at the right time. A subset of patients with the most severe elevations in systemic pro-inflammatory cytokines (e.g. IL-6 levels > 1,000 pg/ml) may benefit from drugs like tocilizumab or anakinra. Still others may benefit from immune stimulation and enhancement of alveolar macrophage function with drugs like GM-CSF which has been shown to boost host immunity against pathogens in critically ill patients without worsening cytokine storm [44, 45]. The design of clinical trials of immune modulators for the treatment of COVID-19 should therefore include prospective immunophenotyping and/or subject stratification based on cell counts, immune function assays, cytokine levels, or other markers of inflammation. Further, we believe that these trials should employ short-acting agents so that protocols can adapt to the dynamic nature of the immune response, as subjects’ immunomodulatory needs may change over time and with the trajectory of their illness. Until data from these clinical trials are available, it will be essential to have equipoise around the use of therapies that target reduction of the immune response, leaving the door open for the use of immunostimulatory therapies in selected patients. Using such an approach we can hope to restore
l lung homeostasis in COVID-19 patients through promotion of 1) alveolar repair to ameliorate acute lung injury, 2) restoration of host defense and 3) balance between pro- and anti-inflammatory responses. A carefully calibrated and personalized treatment approach in COVID-19 has the potential to arrest disease progression and improve outcomes from this devastating illness.
Conflict of Interest

MH is a consultant for La Jolla Pharmaceuticals for whom he provides services that are unrelated to the content of this article. MH is an unpaid advisory committee member for Partner Therapeutics, Inc; reports grants from NIH, and licensing income from Kiadis, outside the submitted work. IJ and LL are employees of Partner Therapeutics, Inc. EEO is co-founder of Tychan Private Limited, that has a direct acting candidate therapeutic antibody against SARS-CoV-2.
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Figure Legend

Figure 1: Dynamic, heterogenous inflammatory processes subsequent to immune escape contribute to disease severity and tissue damage. Early, local inflammatory processes in the lung often result in an effective host response leading to pathogen clearance. In the event of escape of the virus from the immune system as the result of a suppressed or delayed immune response, there is unchecked viral replication. Increased viral load and direct tissue injury precipitate inflammatory processes which lead to highly dynamic and variable local and systemic immune responses. Within the context of COVID-19-induced critical illness, including acute hypoxemic respiratory failure, systemic inflammation (A) and immunoparalysis (B) may occur independently or simultaneously (C). Systemic inflammation, including hypercytokinemia and hyperferritinemia, is common, but is not universally severe. Only a subset of patients have inflammatory biomarkers that are high enough to be consistent with macrophage activation syndrome (MAS) or cytokine release syndrome (CRS)–like presentations. Severe immune suppression (ie, immunoparalysis) may be characterized by decreased antigen presenting capacity and decreased numbers of lymphocytes and natural killer (NK) cells. In sum, COVID-19-induced critical illness is a highly dynamic state with a temporally variable immunophenotype. Heterogeneity of the subsequent inflammatory responses in individual patients is common, and the use of immunomodulatory interventions likely needs to be based on the phase of the response and individual patient immunophenotype.
Figure 1

Effective immune response → Mild disease → Recovery

Immune escape
- Impaired local immune response
- Unchecked viral replication
- Refractory alveolar injury
- Systemic cytokine spillover

COVID-19-induced critical illness

Severe lung disease
Acute hypoxemic respiratory failure

A
Systemic inflammation
Hypercytokinemia
Hyperleukocytosis

B
Immunoparalysis
Antigen presentation
Lymphocytes
NK cells

C
MAS/
"CRS"-like

Dynamic state with a temporally variable immunophenotype