Weak Induction of Interferon Expression by Severe Acute Respiratory Syndrome Coronavirus 2 Supports Clinical Trials of Interferon-λ to Treat Early Coronavirus Disease 2019

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Coronavirus disease 2019 (COVID-19), a respiratory illness caused by a novel coronavirus, was first identified in the Hubei province of China in December 2019 and has now spread worldwide. The etiologic agent of COVID-19 is a β-coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] that is closely related to severe acute respiratory syndrome coronavirus (SARS-CoV), the virus that caused the much more limited SARS outbreak of 2002–2003, and to Middle East respiratory syndrome coronavirus (MERS-CoV), the etiologic agent for MERS. SARS-CoV-2 differs from previous emergent coronaviruses in important ways. The case fatality rate for COVID-19 is considerably lower than that reported for SARS (17%) or MERS (40%) [2]; however, SARS-CoV-2 spread much more rapidly, quickly causing many more total deaths than infection with both previous coronaviruses combined. Currently, there are no effective treatments for COVID-19 and our understanding of the immunological response to SARS-CoV-2 is limited. A report in this issue of Clinical Infectious Diseases from Professor Kwok-Yung Yuen and colleagues demonstrates that SARS-CoV-2 induces very weak expression of interferons (IFNs) in infected cells [3]. This absence of IFN production likely hampers the early innate immune response to SARS-CoV-2 infection.

The authors obtained human lung tissue samples from 6 donors who were not infected with SARS-CoV-2 and divided each sample into 2 subcultures to compare viral replication and immune activation caused by experimental infection with SARS-CoV-2 to that for SARS-CoV [3]. This self-paired design addresses potential random differences between tissue samples that are a problem for small studies. The investigators found that although these 2 coronaviruses have similar cell tropism (types I and II pneumocytes, as well as alveolar macrophages), infection and viral replication was much more efficient for SARS-CoV-2 than SARS-CoV. The higher viral levels associated with SARS-CoV-2 infection may reflect an even more striking observation from this study: SARS-CoV-2 largely failed to induce expression of any IFNs (type I, II, or III) in the infected human lung tissues. While this study does not address how SARS-CoV-2 evades the innate immune response and suppresses endogenous IFN production, these results suggest that treatment with exogenous IFN to stimulate antiviral immunity might be effective against SARS-CoV-2.

IFNs play a crucial role in the immune response to viral infections. Type I IFNs, such as IFN-α and IFN-β, attach to cell surface co-receptors that are expressed ubiquitous. This binding leads to activation of the JAK-STAT signaling pathway and upregulation of numerous IFN-stimulated genes (ISGs). Many of the proteins encoded by these ISGs mediate antiviral activities. The IFN-λ family (also known as type III interferons) [4–6] is a more recently discovered group of cytokines that bind to a distinct receptor complex yet activate the same JAK-STAT signaling pathway. However, expression of the IFN-λ receptor (IFN-λR1) is largely restricted to cells and tissues of epithelial origin, including respiratory epithelial cells [4, 5].

It is increasingly believed that IFN-λs provide important first-line
immunological defense against viral infections of the respiratory tract [7–11]. In murine models, IFN-λs are the first IFNs produced in response to influenza virus infection and these cytokines act at the epithelial barrier to suppress initial viral spread without causing inflammation [9, 11]. Mice lacking IFN-λ1R1 shed more infectious virus particles and transmit the virus to other mice much more efficiently [10]. Intranasal treatment with recombinant IFN-λ inhibits influenza virus replication, protects the upper airways, and blocks virus transmission to uninfected mice [9–11].

Viruses have evolved multiple strategies to interfere with IFN expression and this seems especially true of coronaviruses. In a related previous study, experimental infection with a MERS-CoV strain (human coronavirus EMC) failed to induce expression of type I and type III IFNs in respiratory tissue cultures, while infection with influenza virus induced high levels of both IFN types [12]. In previous work from Professor Yuen’s group, neither MERS-CoV nor SARS-CoV infection induced significant expression of type I IFNs in human monocyte–derived macrophages [13]. The current report from this laboratory, based on their ex vivo human lung tissue model, suggests that IFN expression induced by SARS-CoV-2 is especially weak, even among coronaviruses [3]. For that reason, IFN-λ might be particularly effective against SARS-CoV-2.

There are as yet no data with respect to treatment of SARS-CoV-2 infection with IFN-λ; however, there are relevant data concerning SARS-CoV and MERS-CoV [2]. In macaque monkeys experimentally infected with SARS-CoV, prophylactic treatment with intramuscular pegylated IFN-α reduced viral replication and excretion, as well as pulmonary damage [14]. In a human airway epithelial cell culture model, IFN-λ3 and IFN-λ4 exhibited antiviral effects against MERS-CoV [15, 16]; therefore, IFN-λ might provide similar prophylactic protection against coronavirus infections.

With respect to treatment of established infection, in the aforementioned macaque model, animals receiving pegylated IFN-α after exposure to SARS-CoV had outcomes intermediate between the prophylactically treated group and untreated controls [14]. Most studies of treatment for severe MERS-CoV infection have not shown an association of IFN-α therapy with overall disease outcomes [17]. However, a recurrent theme with all anti-infective drugs is that the time to administration is critical, and that treatment with IFN-α may have been delivered too late to attenuate the very high mortality of MERS-CoV.

Pegylated IFN-λ1, an investigational agent that has undergone testing in > 3000 human subjects, might be an effective early treatment for SARS-CoV-2. In phase 2 and 3 clinical trials of patients with chronic hepatitis C virus (HCV) infection, pegylated IFN-λ1 administered parenterally for up to 48 weeks produced fewer adverse effects, but similar efficacy, compared with pegylated IFN-α [18, 19]. The lower frequency of hematologic adverse events in patients who were treated with pegylated IFN-λ1 vs pegylated IFN-α is consistent with the observation that most hematologic cell types do not express IFN-λ receptors [20]. Despite promising results for the use of pegylated IFN-λ1 in HCV infection, it was abandoned for that indication because of the contemporaneous development of direct-acting antiviral agents for HCV that proved to be even more effective. However, that extensive testing of pegylated IFN-λ1 established its safety, opening the door to its use in other infections. Currently, pegylated IFN-λ1 is being tested for treatment of hepatitis D virus infection, including in a clinical trial now under way at the National Institutes of Health Clinical Center (NCT03600714) [21].

The data on IFN-λ and respiratory infections may have important clinical and public health implications. The SARS-CoV-2 outbreak represents the third time in the 21st century that we have recognized a highly pathogenic coronavirus introduced into the human population and it is likely that there will be more [2]. IFNs are broad antivirals whose effectiveness might be anticipated for such emerging epidemics. The adverse effects of type I IFNs may limit their use for widespread intervention, as is being proposed in the IFN-β plus ritonavir/lopinavir arm of the World Health Organization Solidarity trial [22]; however, adverse effects are notably lower with pegylated IFN-λ1 [18]. Pegylated IFN-λ1 might be deployed early in an outbreak, months or years before specific antivirals or vaccines can be developed and tested.

Preclinical data from various animal model studies suggest that pegylated IFN-λ1 might reduce the disease severity and risk of transmission of SARS-CoV-2. While more specific measures are being developed, this extensively studied agent should be evaluated as part of an early and rapid response to attenuate disease and prevent infection spread. As the pathogenesis of COVID-19 is incompletely understood, both the efficacy and safety of the pegylated IFN-λ1 administration require careful study. An important difference between chronic viral hepatitis, where pegylated IFN-λ1 has been tested so far, and SARS-CoV-2 infection is that patients with severe COVID-19 have a high degree of lung inflammation. While IFN-λ has weaker proinflammatory properties than type I IFN, pegylated IFN-λ1 has not been tested in patients with respiratory infections and, ideally, should be first studied in patients with early SARS-CoV-2 infection or as prophylaxis. Possible trials of pegylated IFN-λ1 for treating more advanced COVID-19 should be informed by those results and include careful monitoring of the inflammatory state of the patients.

Notes

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