Weak Induction of Interferon Expression by SARS-CoV-2 Supports Clinical Trials of Interferon Lambda to Treat Early COVID-19

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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 SARS-CoV-2[1] that is closely related to SARS-CoV, the virus that caused the much more limited SARS outbreak of 2002-2003, and to MERS-CoV, the etiologic agent for the Middle East respiratory syndrome (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 *CID* from Professor Kwok-Yung Yuen and colleagues demonstrates that SARS-CoV-2 induces very weak expression of interferons in infected cells.[3] This absence of IFN production likely hampers the early innate immune response to SARS-CoV-2 infection and suggests that use of exogenous IFN to stimulate antiviral immunity might be successful for treating 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 two 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 two 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 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 ubiquitously. This binding leads to activation of the JAK-STAT signalling 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 signalling pathway. However, expression of the IFN lambda 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-λR1 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 (HCoV-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 amongst 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-1 and MERS-CoV.[2] In macaque monkeys experimentally infected with SARS-CoV-1, 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 anti-viral 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-1 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 over 3,000 human subjects, might be an effective early treatment for SARS-CoV-2. In phase II and phase III 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 to pegylated-IFN-α.[18,19] The lower frequency of hematologic adverse events in patients who were treated with pegylated-IFN-λ1 versus 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 underway 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 WHO 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.

Pre-clinical data from various animal model studies suggest 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 requires 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 less pro-inflammatory 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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TRO'B, LP-O and RPD are coinventors on patents for the IFN-λ4 protein that are held by the National Cancer Institute. All other authors have no potential conflicts to disclose.

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