Editorial

TYPE I INTERFERON: ANTIVIRAL IS NEED OF THE TIME FOR COVID-19

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Since December 2019 the first reported cases in Wuhan China, the global mortality and morbidity of Coronavirus Disease 2019 (COVID-19) has continued to increase.[1] Recently, different types of vaccines are available in clinical use including mRNA, recombinant viral vector-based, inactivated viral, and protein subunit vaccines. These vaccines are developed in urgency that addresses the prevention of COVID-19.[2] Mutation in the severe acute respiratory coronavirus (SARS-CoV-2), poses a high risk to available vaccines with the emergence of multiple variants. The emergence of an extensively mutated Omicron variant is recognized as a highly mutated variant by the World Health Organization (WHO).[3] To date, no approved antiviral agents are available to treat COVID-19 infected patients, the current treatment is only nonspecific and supportive to relieve the patient's symptoms.[4] Effective antiviral agents are needed to treat COVID-19 patients.

More than 2000 clinical and preclinical trials have been conducted on antiviral drugs to identify potential agents for attenuation of COVID-19 virulence. Remdesivir is used as an evidence-based therapy that has shown benefits in the hospital prolong stay and corticosteroid dexamethasone to suppress hyper inflammation in patients with COVID-19.[5,6] Infection caused by a virus, especially novel strains, where patients have little or no proven acquired response to the virus, the affected individual is dependent on the innate arm of the immune system to immolate the disease severity. Interferons (IFN), the main orchestrators of the antiviral immune system with both potent antiviral and immunomodulatory functions, play a critical role in this innate response.[7]

Interferon is, a cytokine family member, induced by viral infection linked up as a primary driver of immune responses in the inhibitory process of viral replication using various effector proteins. Among three types of interferons, type I (IFN- α/β) have an important role in viral protection.[5,8] Type I IFN is most studied against viral infection which is most potent towards SARS-CoV inhibition. Type I IFN was first discovered in response to influenza viral infection about 60 years ago that significantly suppresses replication of the virus. These cytokines provide multiple activities used in patients with cancer, multiple sclerosis, and chronic viral infections.[5]

Like vaccines, there is global interest in existing antivirals being repurposed against COVID-19. In this regard, the role of IFN in COVID-19 needs to be studied to implement rational therapeutic strategies.

IFNs are the principal drugs used in the treatment of hepatitis B, human immunodeficiency, and hepatitis C virus. Due to their wide spectrum potency of cellular targets, they have flue-like side effects. IFN activates the antiviral state in all cells with transcription of the antiviral genes through signal transducers and activators of transcription, Janus kinase-1 and tyrosine kinase-2.[9] Type I IFN are recognized as a promising therapeutic agent based on previous in vivo and in-vitro studies against MERS and SARS-CoV. IFN-β1b shows

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better clinical outcomes in MERS-CoV infected animals by reducing viral load and improving lung pathology. IFN-α improves the oxygen saturation and quickly resolves the radiographic lung injury in patients with SARS-CoV. Similarly in patients with MERS-CoV combination of ribavirin and IFN-α was linked with the improved outcome at 14 days after diagnosis.[8] Lesson learned from previous research on MERS-CoV and SARS-CoV will be important for establishing the efficacy and specificity of type I IFN against COVID-19.

Recently the COVIFERON randomized control trial demonstrated more favorable outcomes in patients treated with IFN. The study noted low mortality in the group that received IFN as compared to the control group.[10] Another double-blind phase-II clinical trial has determined the safety and efficiency of inhaled nebulized interferon beta-1a (SNG001) in the COVID-19 treatment. The outcome of the study showed beneficial effects of SNG001 in asthma and COPD patients seems to be a great improvement for hospitalized COVID-19 patients. Patients taking IFN SNG001 require no more supplemented oxygen.[7] These positive effects seem to be a better choice for patients with severe COVID-19 with possible benefits and an excellent profile. There is a strong logic for advanced trials to also assess the efficacy and safety of IFN in critically ill COVID-19 patients on ventilator support. These findings were limited to a small-scale population which needs further confirmation in large multicenter studies.

Additionally, intranasal administration of type I IFN as a prophylactic agent could have beneficial consequences in high-risk COVID-19 patients. This intranasal prophylactic use could be effective since respiratory viruses infect humans via the nasopharynx.[11] On the other hand, IFN is a potent virus protease inhibitor. IFN also can reduce pulmonary fibrosis caused by a virus that might attenuate acute respiratory distress syndrome (ARDS) in SARS-infected patients.[12] It is noteworthy that SARS-CoV-2 suppresses signaling of IFN-I at the initial stages of infection. Although it was established that early administration of IFN-β demonstrated more promising outcomes in patients with COVID-19.[12]

In severe COVID there is a life-threatening inflammatory pulmonary infection called acute respiratory distress syndrome. There was a drug-drug interaction between corticosteroids and interferon-β that results in increased mortality in patients with ARDS. However, no significant differences were noted in mortality when interferon was administered without corticosteroids. Because both agents participate in different immunological pathways, these findings point to an antagonistic interaction. Interactions between corticosteroids and interferon may result in significant immunosuppression or negate the putative benefits of each drug in ARDS that leads to death.[13] Overlooking these facts is necessary on the interferon-drug interaction, particularly in immunocompromised patients.

Mutation in the SARS-CoV taking vaccine effectiveness at risk, the contraindications of the vaccines are the other concern. Long-term specific protection of the current COVID-19 vaccines is also debated since it was established that anti-SARS-CoV-2 antibodies do not last more than a year. Antibody-dependent enhancement (ADE) is another concern associated with the safety of vaccines.[14] IFNs have opened up unique opportunities for treating the SARS-CoV-2 infection.

We need safe antiviral agents ahead of vaccines to protect the existing patients with COVID-19. In this regard, IFNs are strongly suggested for clinical trials as an antiviral agent for COVID-19. Collaborative global research efforts are needed to establish the safety and effective profile of IFNs in multicentered clinical trials. We are forwarding this information to WHO, CDC, and the scientific community to clarify the use of IFN as a prophylactic\therapeutic agent.

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