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LETTER

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Do interferons play a role in COVID-19?

Letter

The novel coronavirus that emerged in Wuhan, China in December 2019 is the third highly pathogenic human coronaviruses since November 2002.[1] The World Health Organization (WHO) named this virus "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" and the disease "coronavirus disease-19 (COVID-19)."[2] The other two coronaviruses are known as severe acute respiratory syndrome-related coronavirus (SARS-CoV) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV). While the infection is rapidly spreading worldwide, the WHO declared COVID-19 as a pandemic disease on 12 March 2020, only three months after the emergence of the virus. The infection has now become a global concern around the world.[1,2]

Coronaviruses belong to a large family of viruses affecting both animal and human subjects.[3] SARS-CoV and SARS-CoV-2 act through similar mechanisms. The receptor-binding domain of these two viruses shares 72% similarity in the structure.[4] Coronaviruses interact with the human cells through a structural protein known as spike protein.[5] It suppresses the production of type 1 interferones (IFNs) especially IFN-α and IFN-β.[1] IFNs play a vital role here and limit the viral replication before the development of the body adaptive immune responses.[1,6] Interaction of IFNs through the IFN-α/β receptor on infected cells is associated with the expression of different genes. Following phosphorylation of these receptors, the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway will activate. As a result, IFN-stimulated genes (ISGs) will express. ISGs play an important role in antiviral activity of IFNs. Among the ISGs, myxovirus resistance protein A has a potential activity against various viruses. On the other hand, the main consequence of a viral infection is reducing type-1 IFN level in an infected person, which led to a reduction of the innate immune system activity.[6-9] Both IFN-α and IFN-β showed non-specific broad-spectrum antiviral activity against different viruses. These IFNs have been used extensively in the treatment of some viral infections such as hepatitis B and C virus infections. However, IFN-β was more active against SARS-CoV.[7,8]

There are some preclinical (in-vitro and animal studies) and clinical (observational studies) evidence regarding the efficacy of IFNs on SARS-CoA and MERS-CoA viruses.[10-16] The results are controversial and the efficacy of IFNs has not been confirmed yet. Both IFN-α (mostly) and IFN-β were examined. In an in vitro study, IFN-β showed a more potent inhibitory effect on the replication of coronavirus than IFN-α.[11] This may be because of the higher capability of IFN-β to induce the production of MxA protein. Additionally, in a retrospective cohort study, the efficacy of IFN preparations was investigated in MERS-CoV patients. In this study, patients who received IFN-β experienced a lower mortality rate than IFN-α. However, neither of the IFNs preparations (IFN-β1a, IFN-α2a) reduced MERS-CoV mortality significantly. Nonetheless, it should be considered that the results attained from an observational study with a small sample size. Also, older patients with several concomitants comorbidities were included which may be affected response to IFNs.[13]

IFNs did not show any beneficial effect in patients with severe MERS-CoV infection.[10,15,16] It seems that patients with mild to moderate MERS-CoV infections may be considered for treatment with IFNs. However, most of the clinical studies in terms of MERS-CoV were observational. Therefore further randomised clinical trials are needed to evaluate the efficacy of IFNs on MERS-CoV infections.

SARS-CoV-2 may be more sensitive to IFNs in comparison with other coronaviruses. Also, it seems that IFN-β is more effective than IFN-α for the treatment of COVID-19.[17] IFN-β has two subgroups, named IFN-β1a and IFN-β1b. In an in vitro study, antiviral activity of IFN-β1a was 14 times more than IFN-β1b.[14] Therefore, to interpret the efficacy of IFNs, the type of IFN formulation should be considered.

Recently few clinical studies regarding the efficacy of IFNs in the treatment of patients with COVID-19 were published. Early administration IFNs (within 7-10 days after the onset of the symptoms) is critical to fight against coronavirus infections.[18,19] Additionally, in another retrospective multicentre cohort study, early administration of IFN-α2b (≤5 days after admission) was associated with favourable outcome and reduced in-hospital mortality. Whereas, delayed administration of IFN-α2b was associated with increased mortality.[20] As a result of the probable antiviral activity of IFNs in the initial phase of the viral infections, they may be considered as a preventive strategy too. In a prospective, open-label study, 2944 medical staff received nasal IFN-α as prophylaxis against COVID-19 (2-3 drops/nostril/time, four times daily) for 28 days. In the high-risk individuals who had direct exposure with COVID-19 patients, the results were promising. None of them were infected.[21]

In a cohort study, 7, 46 and 24 patients with mild COVID-19 received IFN-α2b alone, IFN-α2b plus arbidol or arbidol alone, respectively. The viral clearance was considered a primary outcome. The administration of IFN-α2b with or without arbidol was associated with better virological response.[22] In another retrospective cohort study, 256 hospitalised patients with moderate to severe COVID-19 pneumonia were enrolled. In-hospital mortality was considered a

primary outcome. In the multivariate analysis, treatment with IFN-β1b did not reduce in-hospital mortality.[23]

Recently, in an open-label, randomised clinical trial 127 patients with confirmed pneumonia because of SARS-CoV2 were included. Patients in the control group received lopinavir/ritonavir 400/100 mg every 12 hours for 14 days. Patients in the treatment group received a 14-day course of lopinavir/ritonavir 400/100 mg every 12 hours and ribavirin 400 mg every 12 hours and three doses of 8 million international units of IFN-β1a every other day. The primary outcome was time for a negative test for SARS-CoV2. The median time to negative test was 7 and 12 days in the treatment and control groups, respectively. Therefore, IFN-β1a as add-on therapy caused a more rapid virological response and shorter duration of hospitalisation.[24] In another randomised clinical trial, the efficacy and safety of IFN-β1a in severe COVID-19 patients were evaluated. In this study, the primary outcome was time to clinical response. Secondary outcomes were complications during hospitalisation and mortality. Forty-two patients and 39 patients were included in treatment and control groups, respectively. Patients in the control group have received standard of care and patients in the treatment group received IFN-β1a plus the standard of care. The dose of interferon was 12 million IU as subcutaneous injections three times weekly for two weeks. Although the time to clinical response was not significantly different but 28-day overall mortality was significantly lower in the IFN group than in the control group. Furthermore, the early administration of IFN (within 7-10 days after onset of symptoms) has been associated with significantly lower mortality compared with the late administration.[19]

Supportive care is the cornerstone of the treatment for COVID-19. However, some broad-spectrum antivirals may be helpful.[2] Various combinations of lopinavir/ritonavir, chloroquine phosphate, oseltamivir, arbidol and ribavirin are under examination.[2,25]

According to the evidence, one of the potential treatment options for COVID-19 is recombinant human interferons (rhIFNs).[10,13,15,16] Considering pharmacodynamics and pharmacokinetic characteristics, these compounds have lower cardiovascular adverse effects and weaker drug interactions than under-trial medications. Flu-like symptoms (fever, fatigue, chills and myalgia) are the common adverse effects.[7,26,27] Serious adverse effects such as neutropenia, thrombocytopenia, hyper- and hypothyroidism, pancreatitis and irreversible pulmonary hypertension have also been reported with IFNs. Nevertheless, most of them were reported following prolonged administration of IFNs.[7] The duration of IFNs administration for COVID-19 is shorter than other indications.

In the recent version of the NIH guideline, the use of IFNs is not recommended in the treatment of patients with severe or critical COVID-19 unless in clinical trials. Also because of insufficient data no recommendation was made either for or against the use of IFNs in treatment of patients with mild to moderate COVID-19.[28]

In the IDSA guideline, no clear recommendation regarding the use of IFNs in the treatment of COVID-19 was provided. Nevertheless, it was noted that early administration of IFNs in combination with other antivirals may show beneficial effects in some patients with COVID-19.[29,30] Accordingly, further studies are required to confirm the efficacy of IFNs in the treatment of patients with different severity of COVID-19.

1 | CONCLUSION

Considering the pathophysiology of the disease, early administration of rhIFNs especially rhIFN-β1a may be a potential antivirals for the treatment of patients with COVID-19. According to the current evidence, the use of IFNs is not recommended for the treatment of patients with severe or critical COVID-19. There are insufficient data to recommend either for or against the use of IFNs for the treatment of patients with mild or moderate COVID-19.

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