Interferon-β: treatment option against COVID-19

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Abstract

In December 2019, an increasing number of cases of novel coronavirus (2019-nCoV) that were linked to seafood wholesale market have identified in Wuhan, China. Taxonomist declared 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease termed as COVID-19. Importantly, there is no approved drugs or vaccine against SARS-CoV-2. Current review is related to address treatment option for COVID-19. Interferon-β have shown significant activity against previous outbreak of SARS-CoV and MERS-CoV. Faced with an ongoing pandemic of SARS-CoV-2 and lack of effective treatment options, identifying compounds with antiviral activity has become a high priority. Efficacy of these treatments is still unclear. Therefore, final analysis is important to develop better treatment strategies for ongoing pandemic.

Antiviral agents and interferon-β against coronavirus

In late December 2019, a cluster of patients with pneumonia of unknown etiology were identified in Wuhan, Hubei province, China that were epidemiologically linked to a seafood wholesale market.[1] The pathogen has been recognized as a novel-coronavirus (2019-nCoV), later taxonomist declared as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that cause the coronavirus disease 2019 (COVID-19).[2,3] As of May 02, 2020, the ongoing pandemic of SARS-CoV-2 infection has led to 32,67184 laboratory confirmed cases and 2,29971 deaths across the globe.[4] Up to date, neither vaccine nor specific antiviral agent is developed for coronavirus infection, so it is a major issue for scientist to find effective antiviral agent to treat this infection. Scientists are struggling to find antiviral agent to treat this disease. Trials thus far has revealed on some agent including, traditional Chinese medicines, natural products, chloroquine phosphate, ribavirin, arbidol, lopinavir/ritonavir and interferon α that demonstrated preliminary efficacy against SARS-CoV.[5] Scientific attention is required towards specific antiviral agent against COVID-19.

A literature search was performed using database PubMed and Google scholar on previous studies especially studies conducted on previous outbreak of SARS-CoV and MERS-CoV. Search term included SARS-CoV treatment with interferon-β, MERS-CoV treatment with interferon-β, effect of interferon-β on SARS-CoV and, MERS-CoV and antiviral activity of interferon-β on SARS-CoV-2. Case reports, letters and duplicate publication were excluded. We mainly focus on original article that specific to our aims of interest were included. Finally 10 studies were cited that subject to interpretation in current context that are mentioned.

There is relevant information regarding antiviral agent from the previous 2002-03 outbreak of SARS-CoV in China and 2012 outbreak of MERS in Saudi Arabia. In these studies interferon-β were potent inhibitors that show in-vitro antiviral activity against SARS-CoV with 50% inhibitory concentration (IC_{50}) value of 500 IU/mL.[6] Interferon-β showed Strong anti-MERS-CoV activity with an IC_{50} value of 1.37 U mL^{-1} and IC_{90} value of 38.8 U mL^{-1}. This result provides strong support for the usage of Interferon-β against SARS-CoV.[7] On the basis of these information it is acknowledged that Interferon-β may be a potent inhibitor of SARS coronavirus-2 replication.

Interferons-β have broad spectrum antiviral efficacy against Ribonucleic acid (RNA) viruses, which act by mediating adaptive immune response with induction of an antiviral response.[8] IFNs play a major role in patients with various respiratory infection due to their immunomodulatory properties. The role of Interferons in the treatment of idiopathic pulmonary fibrosis have significant. Interferon decrease messenger RNA levels of pro-fibrotic cytokines transforming growth factor (TGF-β1), so reduced expression of TGF-β1 cause reduction in amount of fibrosis.[9] Interferons-β production leads to induction of interferon stimulated genes which encode for a various antiviral activity.[10] Clinically Interferons-β have been approved for use in the therapy of hepatitis B and hepatitis C viral infections. Additionally interferons-β are currently assessed in a clinical trial to treat MERS coronavirus and therefore it is suggested for the treatment of COVID-19.[11]

Other coronaviruses MERS-CoV and SARS-CoV are closely related to SARS-CoV-2 that showing similar properties but some variation in their pathology, epidemiology and some of their proteins.[12] Interferons-I therapy has been studied against SARS-CoV and MERS-CoV. IFN-β1a or IFN-β1b are the most potent inhibitor of SARS-CoV and MERS-CoV. Administration of Interferons-β have protective activity in the lung by regulating cluster of differentiation-73 (CD-73) in lung endothelial cells with maintenance of endothelial barrier function and secretion of anti-inflammatory adenosine.[11] IFN-β exhibit strong efficacy, with EC_{50} value of 1.37 to 17 IU/mL against MERS-CoV replication. Similarly to lopinavir/ritonavir, clinical improvements with Interferons-β were observed in MERS-CoV infection.[13] Further studies should be performed to clarify the potential clinical benefit of prescribing Interferons-β for coronavirus infections. Still, the efficacy of these therapy is still unknown against SARS-CoV-2. Therefore, additional studies are needed to clarify the potential clinical benefit of IFN-β against COVID-19.

In some cases, interferon is pathogenic. Delayed interferon-Beta treatment failed to potentially inhibit viral replication, failed to increase the activation of macrophages, neutrophils in the lungs and increased pro-inflammatory cytokine expression result in severe viral lung infection such as fatal pneumonia. In this context, IFN-b or combined therapy may need to be used cautiously in the therapy of viral infections in clinical backgrounds.[14] Interferon-β result in adverse clinical events such as fatigue, depression, sense of weakness, headache and skin infection in patient with multiple sclerosis.[15] Importantly, Interferon-β exhibit effective antiviral activity at doses that have already been shown to have acceptable safety profiles.[6] Interferon is not exempted from side effects, that may be require reducing dosage or ceasing treatment but the mechanism of side effect is not fully understand.[8] So it would be a major advance if the researcher could identify the possible mechanism by which interferon produce side effect against SARS-CoV-2.

Acute respiratory distress syndrome (ARDS) is a life-threatening inflammatory pulmonary process that also result from coronavirus disease 2019. Drug-drug interaction between interferon-β and corticosteroids were noted that lead to increased mortality in patients with acute respiratory distress syndrome (ARDS). However administration of interferon-β without corticosteroids was noted to having no significant differences in mortality. These result imply an antagonistic interaction, since both agents participate in various immunological pathways. Drug-drug interaction between corticosteroids and interferon-β may result in a significant synergy immunosuppression or negates the putative benefits of each drug in ARDS that cause death.[16] Additional study are needed on interferon-β drug-drug interaction especially in immunocompromised patients.

Interferon-β have superior antiviral activity compared with lopinavir and ritonavir against MERS-CoV. Interferon-β possess anti-MERS-CoV activity with EC_{50} value of 175 international units (IU)/mL alone and EC_{50} value of 160 IU/mL in combination with lopinavir and ritonavir that was indistinguishable from that of IFN-β alone. However combination of IFN-β with LPV/RTV improves pulmonary function, so the combination therapies will likely promote restoration and repair of pulmonary homeostasis.[17]

Current study suffers from some notable limitations with lack of experimental investigations on antiviral compounds and little is known about aspect of Covid-19 and Interferons-β. It is rational for the use of interferons-β to treat infections with SARS-CoV-2. IFN-β represent a good safety profile in the treatment of some viral infection.[18] The option of using IFN-β in the therapy of SARS-CoV-2 should be evaluated that may be account for a safe therapy against COVID-19.

As the pandemic spreads, it results in rising mortality around the globe but scientists are searching to identify potential antiviral agent to combat COVID-19. In present there is lack of effective treatment options against COVID-19. So the efficacy and safety profile of interferons-β in the therapy of SARS-COV-2 is technically demanding that need to be investigated in further clinical trials. These study suggest that analysis of interferons-β are of great value for the treatment of this emerging disease.

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020 [Epub ahead of print].
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020 [Epub ahead of print].
3. Jiang S, Shi Z, Shu Y, et al. A distinct name is needed for the new coronavirus. Lancet 2020 [Epub ahead of print].
4. WHO. Coronavirus disease 2019 (COVID-19) situation report - 103. May 02, 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200502-covid-19-sitrep-103.pdf?sfvrsn=d95e76d8_4 Accessed: May 03, 2020.
5. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14:58-60.
6. Hensley LE, Fritz EA, Jahrling PB, et al. Interferon-β 1a and SARS coronavirus replication. Emerg Infect Dis 2004;10:317.
7. Hart BJ, Dyall J, Postnikova E, et al. Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. J General Virol 2014;95:571.
8. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunol Rev 2004;202:8-32.
9. Antoniou KM, Ferdoutsis E, Bouros D. Interferons and their application in the diseases of the lung. Chest 2003;123:209-16.
10. Schoggins JW, Rice CM. Interferon-stimulated genes and their antiviral effector functions. Curr Opin Virol 2011;1:519-25.
11. Sallard E, Lescure FX, Yazdanpanah Y, et al. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res 2020:104791.
12. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 2020:105924.
13. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother 2020;64:5.
14. Channappanavar R, Fehr AR, Zheng J, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Investig 2019;129:9.
15. Knobler RL, Greenstein JI, Johnson KP, et al. Systemic Recombinant Human Interferon-β Treatment of Relapsing-Remitting Multiple Sclerosis: Pilot Study Analysis and Six-Year Follow-Up. J Interferon Res 1993;13:333-40.
16. Mammen MJ, Aryal K, Alhazzani W, et al. Interferon-β-1a for patients with moderate to severe acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. Polish Archiv Intern Med 2020 [Epub ahead of print].
17. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Commun 2020;11:1-4.
18. Festi D, Sandri L, Mazzella G, et al. Safety of interferon β treatment for chronic HCV hepatitis. World J Gastroenterol 2004;10:12.