Interferon beta-1b for COVID-19

Published Online
May 8, 2020
https://doi.org/10.1016/S0140-6736(20)31101-6

See Online/Articles
https://doi.org/10.1016/S0140-6736(20)31042-4

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global epidemic with more than 3 million confirmed cases and 200 000 deaths worldwide thus far.[1] Several drugs with antiviral activity against SARS-CoV-2 have been tested in vitro as well as in ongoing human studies.[2]

Existing literature on the efficacy of different treatments for 2003 SARS-CoV and 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) provides some insight into options for potential repurposing of these drugs for SARS-CoV-2 treatment. Clinical studies on the efficacy of type I interferons, including interferon alfa and interferon beta, in the treatment of SARS-CoV had variable results.[3,4] Additionally, studies on the effects of these treatments on survival of patients with MERS-CoV have not shown significant benefits.[5,6] SARS-CoV-2 triggered lower type I interferon responses than SARS-CoV in an ex-vivo study in human lung tissue[7] and was found to be more susceptible to type I interferons than SARS-CoV.[8]

In *The Lancet*, Ivan Fan-Ngai Hung and colleagues[9] present the results of an open-label, randomised, phase 2 trial that examined the effect of a triple combination regimen of interferon beta-1b 8 million international units (0·25 mg) on alternate days, lopinavir 400 mg plus ritonavir 100 mg every 12 h, and ribavirin 400 mg every 12 h, compared with lopinavir 400 mg plus ritonavir 100 mg every 12 h alone. The investigators enrolled 127 patients with COVID-19 admitted to six hospitals in Hong Kong. Median age of patients was 52 years (IQR 32–62) and 68 [54%] were men; 86 were assigned to the combination group and 41 to the control group. Treatment duration was 14 days. Interferon beta-1b was given in the combination group only to patients who were enrolled less than 7 days after onset of symptoms, for a maximum of three doses by the end of the first week of symptoms.

The primary endpoint was time to negative nasopharyngeal swab for SARS-CoV-2 RT-PCR and secondary endpoints were time to symptom resolution by achieving a national early warning score 2 (NEWS2) of 0, a sequential organ failure assessment (SOFA) score of 0, 30-day mortality, and duration of hospital stay.

Triple therapy was associated with a significant reduction in the duration of viral shedding (time to negative nasopharyngeal swab 7 days [IQR 5–11] in the combination group *vs* 12 days [8–15] in the control group; hazard ratio [HR] 4·37 [95% CI 1·86–10·24]), symptom alleviation (time to NEWS2 0 of 4 days [IQR 3–8] *vs* 8 days [7–9]; HR 3·92 [1·66–9·23]), and duration of hospital stay (9·0 days [7·0–13·0] *vs* 14·5 days [9·3–16·0]; HR 2·72 [1·2–6·13]). This significant difference was sustained in a subgroup analysis of patients who were enrolled within less than 7 days of symptom onset (52 patients in the combination group, who received interferon beta-1b, *vs* 24 in the control group) but not in the subgroup of patients enrolled later than 7 days from symptom onset (34 patients in the combination group, who only received lopinavir–ritonavir and ribavirin, *vs* 17 in the control group).

Most published studies so far have been retrospective or observational. Therefore, this prospective, randomised controlled design adds notable value to the growing evidence on treatments, eliminating a number of limitations inherent to retrospective studies. Additionally, despite the relatively small number of patients in the interferon beta-1b subgroup, significant differences in outcomes were demonstrated. Therefore, this study provides much needed data on a potential therapeutic regimen for SARS-CoV-2.

It is important to note that the studied population had mild or moderate disease at the time of enrolment, evidenced by a median NEWS2 of 2 and SOFA score of 0, and there was no mortality in either group. Whether

Associated Press

similar results are reproducible in populations with severe COVD-19 is unknown and should be explored in future studies.

Although lopinavir–ritonavir was not efficacious in treating SARS-CoV-2 in a recent trial,[10] it is unknown whether this might be partly related to delayed enrolment (median 14 days from symptom onset). The use of placebo as a control in the absence of proven effective therapy is therefore ideal. Additionally, earlier enrolment to standardise the number of interferon beta-1b doses is important but might be impractical, particularly because patients might not present to hospitals earlier than 7 days, when symptoms typically worsen.[11]

This study presents a step towards finding a much-needed therapy for SARS-CoV-2. However, as the authors acknowledge, future studies to examine the efficacy of interferon beta-1b alone or in combination with other drugs to treat severe or critically ill patients with confirmed COVID-19 compared with placebo are warranted.

I declare no competing interests.

Sarah Shalhoub
sarah.shalhoub@lhsc.on.ca

Schulich School of Medicine and Dentistry, Western University, London, ON N6A 5C1, Canada

1 WHO. Coronavirus disease 2019 (COVID-19). Situation report 100. Geneva: World Health Organization, April 29, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200429-sitrep-100-covid-19.pdf?sfvrsn=bbfbf3d1_6 (accessed April 30, 2020).

2 Shi X, Lu Y, Li R, et al. Evaluation of antiviral therapies for coronavirus disease 2019 (COVID-19) pneumonia in Shanghai, China. *J Med Virol* 2020; published online April 16. DOI:10.1002/jmv.25893.

3 Chu CM, Cheng VCC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:** 252–56.

4 Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003; **52:** 715–20.

5 Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis* 2020; **70:** 1837–44.

6 Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis* 2014; **14:** 1090–95.

7 O'Brien TR, Thomas DL, Jackson SS, Prokunina-Olsson L, Donnelly RP, Hartmann R. Weak induction of interferon expression by SARS-CoV-2 supports clinical trials of interferon lambda to treat early COVID-19. *Clin Infect Dis* 2020; published online April 17. DOI:10.1093/cid/ciaa453.

8 Loukugamage KG, Schindewolf C, Menachery VD. SARS-CoV-2 sensitive to type I interferon pretreatment. *bioRxiv* 2020; published online March 9. DOI:10.1101/2020.03.07.982264 (preprint).

9 Hung IF-N, Lung K-C, Tso EY-K, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; published online May 8. https://doi.org/10.1016/S0140-6736(20)31042-4.

10 Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; published online March 18. DOI:10.1056/NEJMoa2001282.

11 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.