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Interferon beta-1b for COVID-19

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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 tissue⁷ and was found to be more susceptible to type I interferons than SARS-CoV.⁸

In *The Lancet*, Ivan Fan-Ngai Hung and colleagues⁹ 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 similar results are reproducible in populations with



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severe COVID-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

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Hypertension, renin-angiotensin-aldosterone system inhibition, and COVID-19

Few could have imagined that hypertension and its treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS) would become a hot topic during the global COVID-19 pandemic. Two factors have contributed to this: first, the observation that hypertension is one of the most common comorbidities associated with severe cases of COVID-19 in patients who have been admitted to hospital and their risk of death;¹ and second, that like the severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 infects cells via specific binding to angiotensin-converting enzyme 2 (ACE2), which is ubiquitously expressed in the lung and other tissues.² These factors have fuelled speculation that use of RAAS inhibitors, particularly ACE inhibitors or angiotensin-receptor blockers, could lead to increased expression of ACE2 in the respiratory tract, thereby increasing the risk of both becoming infected and

developing severe life-threatening complications due to COVID-19. The fact that no evidence supports any aspect of this speculation mattered little as the hypothesis gained traction, initially via social media and subsequently via the medical press.³ Anxiety among patients and physicians has been profound because ACE inhibitors and angiotensin-receptor blockers are the foundation of drug treatment for hypertension, heart disease, and chronic kidney disease, and are among the most widely prescribed drugs globally. Patients have subsequently been withdrawing and substituting these treatments, prompting international cardiovascular and hypertension specialist societies to issue statements of reassurance, while acknowledging the lack of high-quality data to refute the increasing alarm.

This debate, fuelled by speculation, has at last become enriched by data, with the publication of several observational cohort studies.^{4–10} In *The Lancet*,



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