Clinical trial finds inhaled immune response protein increases odds of recovery for hospitalised COVID-19 patients

November 13 2020

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Hospitalised COVID-19 patients in the UK who received an inhaled form of interferon beta-1a (SNG001) were more likely to recover and

less likely to develop severe symptoms than patients who received a placebo, according to a new clinical trial published in *The Lancet Respiratory Medicine* journal. This is the first evidence published in a peer-reviewed medical journal that inhaled interferon beta-1a could lessen the clinical consequences of COVID-19 and serves as proof-of-concept that this treatment could help hospitalised patients recover, but further research is required.

As the number of COVID-19 infections continues to rise around the world, there is a pressing need to develop new treatments for the more severe and life-threatening symptoms such as pneumonia and respiratory failure.

Interferon beta is a naturally occurring protein that coordinates the body's immune response to viral infections. Laboratory studies have found that the SARS CoV-2 virus directly suppresses the release of interferon beta, while clinical trials demonstrate decreased activity of this important protein in COVID-19 patients. The formulation of interferon beta used in this new study—SNG001—is directly delivered to the lungs via inhalation and has been trialled in the treatment of asthma and chronic obstructive pulmonary disease (COPD). This study aimed to evaluate the safety and efficacy of SNG001 to treat hospitalised COVID-19 patients.

The trial was conducted at nine UK hospitals with patients who had a confirmed SARS-CoV-2 infection. It compared the effects of SNG001 and placebo given to patients once daily for up to 14 days, and followed up patients for a maximum of 28 days after starting the treatment. Patients were recruited from March 30 to May 30, 2020, and were randomly assigned to receive the treatment or a placebo. All members of the research team were blinded to which group the patients were allocated. During the study, changes in the clinical condition of patients were monitored.

Of the 101 patients enrolled in the study, 98 patients were given the treatment in the trial (three patients withdrew from the trial) - 48 received SNG001 and 50 received a placebo. At the outset of the trial 66 (67%) patients required oxygen supplementation at baseline (29 people in the placebo group and 37 in the SNG001 group). Patients who received SNG001 were twice as likely to show an improvement in their clinical condition at day 15 or 16, compared with the placebo group.

In the placebo group, 11 (22%) of 50 patients developed severe disease (defined in this study as requiring mechanical ventilation) or died between the first dose and day 15 or 16, compared with six (13%) of 48 patients who received SNG001 (this includes three deaths in the placebo groups and none in the treatment group).

Over the 14-day treatment period, patients who received SNG001 were more than twice as likely to recover, compared to those in the placebo group—with 21 (44%) patients in the SNG001 group recovering compared with 11 (22%) patients in the placebo group (patients were deemed to have recovered when they were no longer limited in their activity). In a secondary analysis, the authors found that at 28 days, SNG001 patients were over three times more likely to recover than patients receiving placebo.

Lead author, Professor Tom Wilkinson from the University of Southampton, UK, says: "The results confirm our belief that interferon beta, a widely known drug approved for use in its injectable form for other indications, may have the potential as an inhaled drug to restore the lung's immune response and accelerate recovery from COVID-19. Inhaled interferon beta-1a provides high, local concentrations of the immune protein, which boosts lung defences rather than targeting specific viral mechanisms. This might carry additional advantages of treating COVID-19 infection when it occurs alongside infection by another respiratory virus, such as influenza or respiratory syncytial virus

(RSV) that may well be encountered in the winter months."

The safety of inhaled interferon beta-1a was assessed by monitoring adverse events over 28 days. 26 (54%) patients in the SNG001 group and 30 (60%) patients in the placebo group had adverse events during treatment, with the most frequently reported being headache. Fewer patients in the SNG001 group had serious adverse events, compared with the placebo group.

The authors note some limitations of their study. The sample size was small and, as such, findings cannot be generalised to wider populations and healthcare settings. There were differences between the two groups at recruitment: patients in the SNG001 group had more severe disease at baseline and more patients had hypertension, and in the placebo group more patients had diabetes and cardiovascular disease. However, these factors were considered in the statistical model used, and beneficial signals for therapy were enhanced when a priori adjustments were made. Larger trials should be able to address these limitations with randomisation of more varied groups, according to the researchers.

The same research group is also assessing the effectiveness of the treatment in pre-hospital cases of COVID-19. To assess the treatment for patients who are critically ill and requiring mechanical ventilation, an alternative delivery method than the current nebuliser is needed.

Writing in a linked Comment, lead author Nathan Peiffer-Smadja (who was not involved in the study), from Assistance Publique—Hôpitaux de Paris, France, pointed out that preliminary results from the SOLIDARITY/DisCoVeRy randomised clinical trial in COVID-19 patients (which includes 8% who were mechanically ventilated) has so far failed to show efficacy of subcutaneous injectable interferon beta-1a. One potential explanation is because this route of administration doesn't provide the targeted delivery of the drug to the lungs, which occurs with

inhaled delivery. The Comment also highlights concerns that in severe COVID-19 patients the use of the drug could increase the inflammatory response and be associated with safety issues.

He says: "The number of patients enrolled in this pilot clinical trial is of course small. In addition, this study neither showed any impact of the evaluated treatment on time to discharge nor on mortality, although the study was obviously not powered to respond to the latter question. Larger randomised clinical trials are therefore needed to confirm these results. The safety of nebulised interferon beta-1a will be of special interest since nebulisation of interferon has no marketing authorization for any indication yet. These trials should aim to evaluate the effect of interferon beta-1a on inflammatory biomarkers and virological data to better characterise the physiopathology underlying the use of this drug. It will also be interesting to study whether there is an impact of interferon beta-1a on prolonged symptoms, especially pulmonary."

More information: Phillip D Monk et al, Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial, *The Lancet Respiratory Medicine* (2020). DOI: 10.1016/S2213-2600(20)30511-7

Provided by Lancet