

Inhaled therapies for COVID-19

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SARS-CoV-2 is a coronavirus that infects epithelial cells in the naso- and oropharynx before infecting epithelial cells of the lower airways and alveoli and in severe COVID-19 spreading systemically and inducing a systemic inflammatory response. SARS-CoV-2 is spread mainly by virus particles in droplets and aerosols. This suggests that inhaled therapies may be useful in the treatment of early COVID-19 disease before severe respiratory systemic features develop and potentially in reducing transmission of the virus in the community. To be effective any inhaled therapy must be rapidly acting to prevent viral replication in respiratory epithelial cells to prevent the disease spreading down the respiratory tract and into the systemic circulation. It also needs to be safe and available for early prescription in order to prevent severe disease and hospitalisation. The development of inhaled therapies for COVID-19 may involve repurposing of existing inhaled therapies or developing inhaled formulations of new drugs with antiviral effects.

Patients with asthma and COPD were reported to be less likely to be hospitalised with SARS-CoV-2 infection despite the concern that this coronavirus would have severe consequences for these patients as coronaviruses are known to trigger severe exacerbations. One possibility was that this may be due to the widespread treatment with inhaled corticosteroids (ICS), which are known to suppress ACE2 and TMPRSS2 on epithelial cells that are key entry receptors for the virus and also reduce virus replication *in vitro*. A community based open label parallel group phase 2 study of the ICS budesonide (800 µg bid until recovery) in people with early symptoms (within 7 days of onset) of COVID-19 and confirmed by PCR testing (STOIC) showed that only 1/69 people in the ICS group developed severe disease compared with 10/70 in the usual care group.¹ Clinical recovery was also shorter in the ICS group. This finding was confirmed in an open label study of inhaled budesonide in individuals over the age of 65 years at risk from severe COVID-19 (PRINCIPLE), which showed a reduction in time to recovery and a trend towards reduced hospitalisation and death.² Several other trials, including double-blind studies, of ICS in early COVID-19 are currently underway with different corticosteroids, including ciclesonide, which appears to be the most effective against SARS-CoV-2 *in vitro*.³ However, a recent double-blind study of nasal and inhaled ciclesonide failed to show any benefit in early COVID-19, although the population was mainly young adults who have a low risk of disease progression.⁴ The mechanism of action of ICS in COVID-19 has not yet been established, but may involve reduced viral entry due to suppression of ACE2 and TMPRSS2 in airway epithelial cells, reduced viral proliferation or reduced inflammatory mediators secreted by airway epithelial cells that may promote viral spreading.

Interferon β 1 is currently approved for treating multiple sclerosis. Nebulised IFN- β 1a (SNG001) gave a greater degree of clinical improvement in hospitalised COVID-19 patients and a reduction on symptoms (mainly dyspnoea) compared to with placebo and was well tolerated.⁵ However, studies in early disease are underway but have not yet been reported, although there are logistical problems in the need for a nebuliser to deliver the drug. Inhaled PUL-42 is a combination of a TLR2/6 and a TLR9 inhibitors which is effective in a single inhaled dose against SARS-CoV and MERS-CoV infection in mice and reduces the lung viral load.⁶ This drug is now in clinical trials for COVID-19. Other inhaled drugs, including antivirals such as remdesivir and niclosamide, are also in development.