Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

variable immune effects.[8] Future research could evaluate the use of low-dose antiplatelet drugs in patients with infection to prevent their deterioration to sepsis. Likewise, it might be worth investigating the benefit and risk of secondary prevention of sepsis with antiplatelet drugs in patients who survived a first episode of sepsis. ANTISEPSIS is a pioneering study in the field of sepsis suggesting that aspirin probably does not prevent sepsis-related death.

I declare no competing interests.

Djillali Annane
djillali.annane@aphp.fr

Service de médecine intensive réanimation, Hôpital Raymond Poincaré, Laboratory of infection and inflammation U1173 Université Paris Saclay-UVSQ, INSERM, RHU-RECORDS, FHU-SEPSIS, 92380 Garches, France

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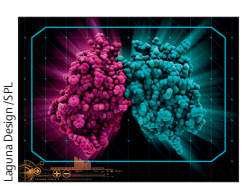
Nebulised interferon beta-1a for patients with COVID-19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In *The Lancet Respiratory Medicine*, Phillip Monk and colleagues[1] report the results of a randomised, double-blind, placebo-controlled phase 2 pilot trial of nebulised interferon beta-1a in 101 adults admitted to hospital with COVID-19. The authors found that patients who received nebulised interferon beta-1a had significantly greater odds of clinical improvement across the WHO Ordinal Scale for Clinical Improvement than those who received placebo, both on day 15/16 (odds ratio [OR] 2·32 [95% CI 1·07–5·04]; p=0·033) and on day 28 (3·15 [1·39–7·14]; p=0·006). However, there was no significant difference between treatment groups in the odds of hospital discharge by day 28: 39 (81%) of 48 patients had been discharged in the nebulised interferon beta-1a group compared with 36 (75%) of 48 in the placebo group (OR 1·84 [95% CI 0·64–5·29]; p=0·26).

Type 1 interferons are among the first cytokines produced during a viral infection and promote both innate and adaptive immunity. Interferon beta has shown an antiviral effect against coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in in-vitro studies and animal models.[2] A recently published randomised clinical trial found that a combination of recombinant interferon beta-1b and lopinavir–ritonavir decreased mortality in patients with MERS-CoV infection.[3] Clinical studies of SARS-CoV-2 found that a proportion of patients with severe COVID-19 had impaired type I interferon activity,[4] potentially linked to autoantibodies against type I interferon.[5] However, preliminary results from the SOLIDARITY/DisCoVeRy randomised clinical trial in more than 2000 patients showed no efficacy of subcutaneous interferon alone or with lopinavir–ritonavir.[6] The results of the present pilot study,[1] in contrast to the results of the SOLIDARITY trial, corroborate findings from in-vitro studies and animal models showing that the interferon pathway is crucial in controlling SARS-CoV-2 infection.

How can we account for these apparently conflicting results? First, the population targeted by these studies was different. The population in the present pilot study[1] was overall at a less severe stage of COVID-19 than that in the SOLIDARITY trial; no patients with invasive ventilation were included, whereas 8% of patients in SOLIDARITY were ventilated; and global mortality was 3% at 28 days in the present study

versus 12% in SOLIDARITY. Second, the route of administration of interferon beta-1a was different in these studies: the present study used nebulised therapy that delivers interferon beta-1a directly to the respiratory tract, whereas the SOLIDARITY trial used subcutaneous interferon beta-1a. Nebulised therapy allows targeted delivery of interferon to the lungs, where it can induce the expression of interferon-stimulated genes that participate directly (eg, through degradation of viral RNA, interference with viral translation or assembly, and so on) or indirectly (via signalling and recruitment of monocytes or macrophages or T cells, increased antigen presentation and cross-presentation, and so on) in the antiviral response in the mucosa.[7]

The number of patients enrolled in the present study was small. Additionally, this study showed no impact of the evaluated treatment on time to discharge or on mortality, although the study was not adequately powered to analyse mortality outcomes. Larger randomised clinical trials are therefore needed to further investigate the effectiveness of nebulised interferon beta-1a therapy in this setting. The safety of nebulised interferon beta-1a will be of special interest since nebulisation of interferon has no marketing authorisation for any indication yet. Future trials should evaluate the effect of interferon beta-1a on inflammatory biomarkers and analyse virological data to better characterise the physiopathology underlying this drug. It will also be worthwhile to investigate whether interferon beta-1a has an impact on prolonged symptoms of COVID-19, especially pulmonary symptoms. Recent studies have found persistent dyspnoea in up to 40% of patients with COVID-19 at 2 months after disease onset[8] and abnormalities in pulmonary function at 3 months. In light of the growing number of patients with SARS-CoV-2 infection, it is now crucial to find drugs that could prevent these pulmonary sequelae. Other issues that should be explored include the price and availability of interferon beta.

It is also important to define which population should be prioritised in subsequent large randomised clinical trials. To optimise the antiviral effect of interferon beta, there is a greater rationale to target patients at an early stage of the disease. Studies in mice with MERS-CoV infection have shown that the timing of type I interferon administration in coronavirus infections has a crucial role: antiviral effects were observed if type I interferon was administered shortly after infection, but type I interferon failed to inhibit viral replication and had side-effects when administered later.[9] In patients with severe COVID-19, an exacerbated inflammatory response has been identified as a cause of pulmonary complications, and interferon beta-1a—a pro-inflammatory cytokine—could increase the inflammatory response and be associated with safety issues.[10] Therefore, patients at an early stage of the disease, possibly in the outpatient setting, might be of interest for future randomised clinical trials of nebulised interferon beta-1a.

Despite the large number of clinical trials underway for the treatment of COVID-19, few antiviral drugs against SARS-CoV-2 have been identified. The findings of the present study are promising in this regard. They should be promptly evaluated in large randomised clinical trials, including academically led trials.

We declare no competing interests.

Nathan Peiffer-Smadja, Yazdan Yazdanpanah
nathan.peiffer-smadja@aphp.fr

Infectious Diseases Department, Bichat-Claude Bernard Hospital, Assistance-Publique Hôpitaux de Paris, Paris, France (NP-S; YY); Université de Paris, INSERM, IAME, F-75006 Paris, France (NP-S; YY); and National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK (NP-S)

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