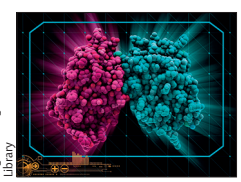
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Subcutaneous interferon beta-1a in COVID-19: raking the ashes of an intervention trial



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There is increasing evidence that the current COVID-19 pandemic will continue to affect global health and economic prosperity for months and possibly years to come. Initial successes in vaccine development and roll-out in several territories have not translated into effective global vaccine coverage, with protection as low as 2% in many countries.[1] Furthermore, recent data from studies in early vaccine recipients suggest fading protective immunity. New variants of concern are also emerging, which are less likely to be covered by current vaccines.[2] In this context, developing new treatments for COVID-19 remains a global health priority. Existing treatments have been established by repurposing drugs that have been shown to be safe for other indications, with a focus on reducing disease severity and mortality in hospitalised patients with severe COVID-19. To date, the selection of candidate therapies has not been informed by an in-depth understanding of disease pathology and, therefore, has tended to focus on broad spectrum anti-inflammatory strategies or repurposed antivirals.

Therefore, the therapeutic administration of an alternative therapeutic strategy for COVID-19 is important. IFNβ is a naturally occurring protein and a key facet of the cellular innate immune response to viral infection. Interferon beta has been widely used in an immunomodulatory capacity for the treatment of multiple sclerosis with a good safety record. An emerging understanding of the pathogenesis of COVID-19 has highlighted a potential key role for interferon beta as a potential treatment, as diminished innate immune responses are associated with the development of severe disease. Furthermore, early reports found that enhanced disease was observed in individuals with genetic defects in type 1 IFN production,[3] and observational studies subsequently indicated that transcriptomic signatures of severe and fatal COVID-19 cases were associated with diminished type 1 IFN responses compared with patients with better outcomes.[4]

Further interest was driven by small interventional studies done early on in the pandemic, indicating the potential clinical utility of interferon beta.[5,6] Although the results of these studies varied, one open-label study showed that the addition of interferon beta to other antivirals was associated with faster recovery of COVID-19 symptoms and reduced duration of hospital admission compared with the other antivirals alone.[6] Furthermore, a randomised, placebo-controlled, phase 2 trial of inhaled interferon beta-1a showed clear signals of efficacy, with a greater odds of improvement in clinical status and faster resolution of symptoms with treatment compared with placebo and, importantly, a good safety profile.[7]

In *The Lancet Respiratory Medicine,* Andre C Kalil and colleagues[8] report the findings of a double-blind, randomised, placebo-controlled trial of injected interferon beta-1a in hospitalised patients with COVID-19. The trial included 969 patients who received remdesivir and up to four doses of either subcutaneous interferon beta-1a or placebo administered every other day. The study showed no signal of efficacy for the primary endpoint of time to recovery; median time to recovery in both groups was 5 days (recovery rate ratio 0·99 [95% CI 0·87–1·13]; p=0·88). Additionally, no significant difference in mortality at day 28 was observed between the two groups (hazard ratio 1·33 [95% CI 0·69–2·55]; p=0·39). Unlike previous trials, patients in the interferon beta-1a plus remdesivir group were more likely to have at least one adverse event compared with the placebo plus remdesivir group, and a greater proportion of patients who required high-flow oxygen at baseline had adverse events after treatment with interferon beta-1a compared with those given placebo. Therefore, despite the potential efficacy signals from earlier studies and a plausible biological rationale for interferon beta treatment for COVID-19, the trial by Kalil and colleagues[8] showed no efficacy signal and highlighted a potential safety issue for subcutaneous therapy in patients with severe disease. However, this observation is a common narrative in recent COVID-19 trials, whereby small, early, uncontrolled studies, which show hopeful signals of benefit, are not subsequently replicated in more definitive, larger scale, and later phase studies. In each case, dissecting the reasons for these inconsistent findings will be key to evolving our understanding of the disease and treatment response.

The scale, design, and use of a placebo control in this trial[8] mitigates this finding being an aberrant result and, consequently, there appears to be no future for subcutaneous interferon beta therapy in hospitalised patients with COVID-19. However, consideration of the trial context and the specifics of drug delivery could be valuable to inform future studies. The standard of care for COVID-19 has evolved rapidly and currently includes the use of systemic steroids following data from the RECOVERY study in June, 2020. The use of systemic steroids is an important consideration in the context of interferon beta treatment because corticosteroids directly affect IFN signalling, not only by reducing transcription of key factors including STAT1 and IRF9,[9] but also by their direct effects on the IFNβ receptor.[10] Therefore, corticosteroids, which were used as standard supportive care, could have abrogated the potential antiviral effects of interferon beta-1a in this trial.[8] Additional considerations are the subcutaneous route of drug delivery. The bioavailability of the drug at key sites of viral replication, especially in the respiratory epithelium, might not have been optimal compared with alternative routes, such as inhalation.[7] This factor could be particularly relevant in the context of pulmonary microvascular pathology leading to perfusion defects, which has been observed in patients with severe disease. These factors combined could have diluted or annulled any potential for beneficial effects of treatment in the study.[8]

The urgent need to develop better therapies for COVID-19 remains, and learnings from negative trials such as this[8] are important. Questioning current treatment strategies and the standards of care included when trials are designed will be key not only to identify efficacious therapies but also to ultimately define an optimised treatment plan for a disease that might continue to be prevalent for years to come.

TW reports being a founder and director of, and a shareholder in, my mhealth, outside of the submitted work; receiving research grants for trials of interferon beta and other COVID-19 treatments from AstraZeneca, GlaxoSmithKline, Synairgen, Bergenbio, UCB, NIHR, UKRI, and my mhealth within the submitted work; receiving consultancy fees from AstraZeneca, Synairgen, my mhealth, Valneva, OM Pharma, Boehringer Ingelheim, and Roche within the submitted work; receiving fees for attending lectures and meetings from Boehringer Ingelheim, AstraZeneca, Chiesi, Teva, and GlaxoSmithKline outside the submitted work; receiving travel support for attending conferences and meetings from Nutricia, AstraZeneca, Chiesi, Boehringer Ingelheim, and GlaxoSmithKline outside the submitted work; applying for patents for bacterial vaccines with GlaxoSmithKline and my mhealth, outside of the submitted work; being a member of a specialist chronic obstructive pulmonary disease advisory group within the submitted work; and being a member of the independent data monitoring committee of a vaccine study sponsored by Valneva and Synairgen within the submitted work.

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COVID-19-related ARDS: one disease, two trajectories, and several unanswered questions

Since the early days of medicine, doctors have described the natural history of disease and its different forms, primarily based on personal interpretation or intuition, in contrast to modern evidence-based medicine. For example, leptospirosis has been described with icterohaemorrhagic or pulmonary subtypes, but the existence of these phenotypes has been confirmed only relatively recently.[1] Recent improvements in analysis and comprehension have been made possible using modern statistical analysis. For example, a previous

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