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## Letter to the Editor

Lack of efficacy of Interferon  $\beta$ -1a in COVID-19 patients with mild to moderate pneumonia

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## Dear Editor,

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2), poses an unprecedented threat for global health. Even in the context of intensified vaccine rollout, identifying efficacious therapeutics remains a priority in case of severe forms of COVID-19. During the early phases of the pandemic, efforts were addressed at investigating repurposed therapeutic agents with antiviral and/or immuno-modulating properties, culminating in a broad multi-arm international trial (WHO SOLIDARITY) testing, among others, Interferon  $\beta$ -1a (IFN $\beta$ -1a) [1], a recombinant pharmaceutical compound of the human cytokine IFN $\beta$  belonging to the type I interferon family. In contrast to evidence from smaller retrospective studies and clinical trials [2,3], the SOLIDARITY and the NIH-sponsored ACTT-3 trial [4] reported no added benefits with IFN $\beta$ -1a in hospitalized patients. A subsequent trial testing higher doses of IFN $\beta$ -1a also demonstrated no efficacy [5].

In the first place, IFN $\beta$ -1a stood as a promising candidate for different reasons. First, IFN $\beta$ -1a displays antiviral activity against SARS-CoV-2 in vitro [6]. Second, defective or dysregulated type I interferon responses have emerged as a hallmark of SARS-CoV-2 infection [7]. Moreover, observational and functional studies have suggested that loss of type I IFN responses, either caused by neutralizing autoantibodies directed against type IFNs [8], or by inherited gene mutations [9], is associated with higher risk of severe COVID-19.

Based on this rationale, between 2020 and 2021, in concomitance with the Solidarity and the ACTT-3 trials, we conducted a single-center, randomized, controlled, open-label, phase 2 clinical trial to evaluate efficacy and safety and antiviral activity of IFN $\beta$ -1a in hospitalized patients with COVID-19 radiologically diagnosed pneumonia (INTERCOP study, NCT04449380; EudraCT 2020-002,458-25).

The study protocol was previously reported [10]. People aged 18 years or older, diagnosed at the Emergency Department of San Raffaele Hospital (Milan, Italy) with COVID-19 by RT-PCR and pneumonia by chest radiography or computed tomography, with a clinical status of non-severe disease as defined by categories 3 and 4 of a 7-point clinical severity ordinal scale, were considered for enrolment. The scale consisted of the following: 1) not hospitalized, with resumption of normal

activities; 2) not hospitalized, but unable to resume normal activities; 3) hospitalized, not requiring supplemental oxygen; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6) hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7) death.

The protocol and consent documents were approved by the Ethics Committees of the San Raffaele Hospital, Milan and of the Lazzaro Spallanzani Institute for Infectious Diseases, Rome, Italy (the national center overseeing COVID-19 clinical trials in Italy) and by the Italian Medicines Agency (AIFA). All patients or their legally authorized representative provided written informed consent. The trial has been conducted in compliance with the principles of the Declaration of Helsinki.

Eligible patients were randomly assigned 2:1 to either receive interferon IFN $\beta$ -1a (Rebif®, Merck Serono, Rome, Italy), 44 micrograms 3-times per week for two weeks, at least 48 h apart in addition to standard of care, or standard of care alone. The experimental drug was administered over a maximum range of 14 days or until negative conversion of nasal swab.

The primary outcome measure was the time to negative conversion of nasopharyngeal swabs for SARS-CoV-2, defined as the date of the first negative, confirmed, nasal swab. Nasopharyngeal swabs were taken every other day from baseline until day 15, then at day 21 and at day 29, as per protocol. The full set of the secondary and exploratory outcomes is reported in the Protocol [10].

Efficacy and safety were evaluated up to day 29. Evaluation was performed during hospitalization and, in case of discharge in the meanwhile, in a dedicated outpatient clinic at weekly intervals. In patients still positive for SARS-CoV-2 infection at day 29, additional nasopharyngeal swabs were offered as extra-follow-up tests and included in the analyses.

Albeit unplanned, an interim analysis was requested by the Principal Investigator at the end of the second epidemic wave and in coincidence with the publication of the interim results of the Solidarity Trial showing no significant clinical effects of IFN $\beta$ -1a in COVID-19 patients.

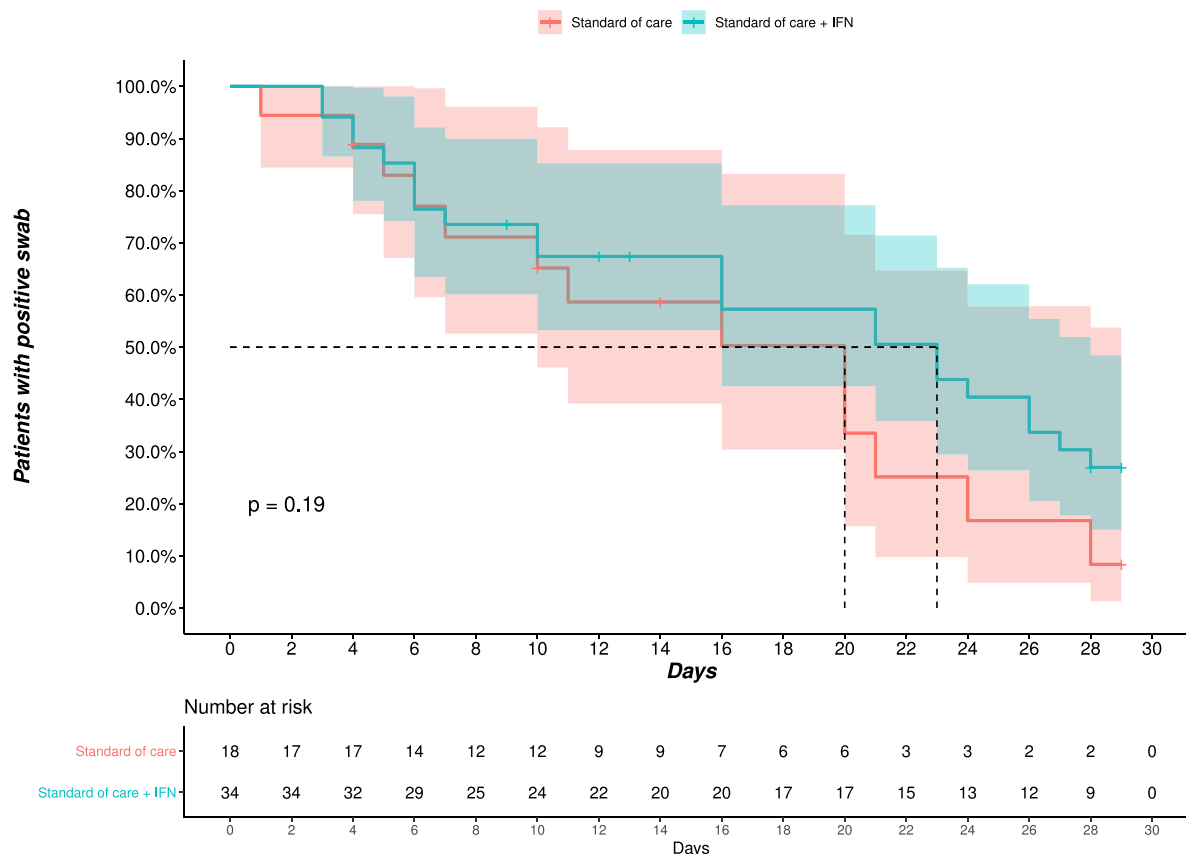
The trial was prematurely terminated for futility: 53 patients (44% of the planned cohort) were recruited at the time of trial termination:

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**Fig. 1.** Time to negative conversion of nasopharyngeal swabs in Covid-19 patients treated with IFN $\beta$ -1a in addition to standard of care vs standard of care alone (shaded areas indicate 95% C.I.).

median age was 67 yr (IQR 51–80), 32 were male, 50 (94%) with no oxygen supplementation and 3 (6%) on low flow oxygen at baseline. There were 4 deaths (7.5% of the total cohort): 2 (5.7%) in the IFN $\beta$ -1a intervention and 2 (11.1%) in the control arm. Median time to negative conversion of nasopharyngeal swabs (primary outcome of the study) was 23 and 20 days in the intervention and control arms, respectively ( $p = 0.19$ ; hazard ratio for negative conversion 0.63 [95% CI 0.32–1.26]) (Fig. 1). No significant differences emerged in the secondary outcomes. Overall, adverse events occurred in 28 (82%) and 6 (33%) patients in the intervention and control arms, respectively, being fever the most commonly event reported.

In conclusion, subcutaneous IFN $\beta$ -1a does not reduce the duration of infection of SARS-CoV-2 and does not ameliorate the clinical course of COVID-19.

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