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Considering Personalized Interferon Beta Therapy for COVID-19

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Davoudi-Monfared et al. (1) report in this journal the results from a clinical trial on coronavirus disease 2019 (COVID-19) patients showing that subcutaneous administration of interferon beta (IFN-β) was associated with a more rapid recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and decreased mortality. These findings have been corroborated by two recent phase 2 clinical trials during which IFN-β was administered, either in combination with lopinavir-ritonavir and ribavirin (2) or alone in a nebulized, inhaled form of the molecule (3). Recombinant IFN-β therapy, in combination with lopinavir-ritonavir, was also associated with reduced mortality in a recently completed randomized clinical trial of hospitalized patients with Middle East respiratory syndrome (MERS) (4). These reports provide a rationale for IFN-β therapy of coronavirus infections associated with acute respiratory syndromes, together with the finding of an impaired type I IFN signature in COVID-19 patients with severe disease (5).

Notwithstanding these results, it should be emphasized that only a subpopulation of COVID-19 patients suffers from a defective type I IFN response (6). Indeed, we show here that among 112 patients with COVID-19 hospitalized at the Pitié-Salpêtrière Hospital in Paris, France, only 35.7% had serum IFN-β levels below the limit of detection at admission (Fig. 1). Moreover, circulating IFN-β levels, when detectable, were significantly higher in patients who died before day 30 than in survivors (mean, 1.79 versus 1.17 pg/ml; $P = 0.02$) (Fig. 1). Mortality was higher ($P = 0.01$) in those patients (7 out of 11 patients; 63.6%) with the highest IFN-β levels ($>$3.4 pg/ml) than in patients with lower IFN-β levels (15 out of 61; 24.6%), as well as in those with IFN-β levels below the limit of detection (11 out of 40; 27.5%) (Fig. 1).

These results might be important to consider in the context of an hyperinflammatory role for type I IFNs in cases of severe COVID-19 (7), as was demonstrated in coronavirus-infected mouse models (8, 9) and in a recently reported case of COVID-19-associated type I interferonopathy (10). In this respect, the timing of IFN-β treatment for COVID-19 patients must be taken into account. Indeed, as shown by Davoudi-Monfared et al. (1), IFN administration during the early phases of SARS-CoV-2 infection results in a favorable clinical outcome. In contrast, late administration ($\geq$5 days after admission) is associated with increased in-hospital mortality, most likely due to an exacerbation of the cytokine storm associated with COVID-19 (11).

Thus, IFN-β therapy might not be recommended for COVID-19 patients with high circulating type I IFN levels or more than 5 days after symptom onset. In addition, we

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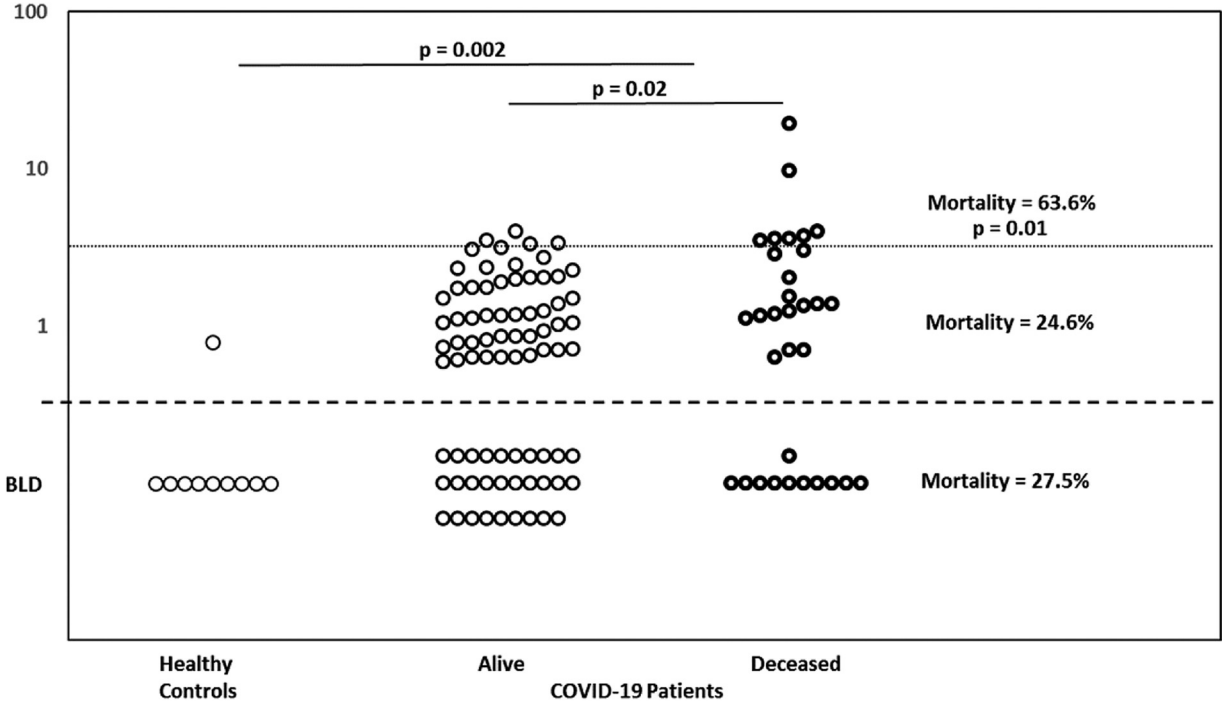

FIG 1 IFN-β levels among healthy controls and COVID-19 patients. Patients ($n = 112$) presenting with a positive SARS-CoV-2 real-time reverse transcriptase-PCR result from their nasopharyngeal swab and pulmonary involvement were included at hospital admission. Mortality was assessed at day 30 after admission. Sampling times from onset of symptoms varied between 0 and 25 days (median, 9 days). Healthy SARS-CoV-2-negative individuals ($n = 10$) were included as controls. For all individuals, sera were stored less than 4 h after collection at −80°C. Serum IFN-β levels were measured by a highly sensitive enzyme-linked immunosorbent assay (ELISA; VeriKine-HS human IFN-β ELISA kit; PBL Assay Science, Piscataway, NJ, USA). Symbols represent individual patients. The dashed line represents the limit of detection (0.59 pg/ml). The dotted line represents the 90th percentile of IFN-β levels (3.4 pg/ml). A *P* value for COVID-19 mortality was calculated for patients with detectable IFN-β levels. The statistical significance of differences between groups was assessed using the nonparametric Mann-Whitney test and the Fisher-exact test. The study was performed at the AP-HP Pitié-Salpêtrière Hospital in Paris, France, and approved by the local ethical committee (approvals CER-SU-2020-21 and -31). BLD, below the limit of detection.

demonstrated, in another rare subset of severe COVID-19 patients, the presence of neutralizing anti-IFN-β autoantibodies (12) that might also interfere with the efficacy of such a biotherapy. Conversely, IFN-β treatment might be of benefit for patients with other anti-type I IFN antibodies, such as neutralizing anti-IFN-α and/or anti-IFN-ω autoantibodies (12).

Although Davoudi-Monfared et al. (1) report a decreased mortality in their clinical trial, it will be important to determine which patients might benefit most from IFN-β therapy in order to further improve personalized treatment. Therefore, we advocate cautious use of IFN-β treatment for COVID-19 that should be conditioned by the inclusion of both type I IFNs and autoantibody profiling in future trials.

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