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Davoudi-Monfared et al. (1) report in this Journal the results from a clinical trial on COVID-19 patients showing that subcutaneous administration of interferon-β (IFN-β) was associated with a more rapid recovery from 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 randomised clinical trial in hospitalized patients with Middle East Respiratory Syndrome (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 Pitié-Salpêtrière in Paris, 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 deceased before day 30 as compared to survivors (mean 1.79 *vs* 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), as compared to patients with lower IFN-β levels (15 out of 61; 24.6%), as well as 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 severe COVID-19 (7), as demonstrated in coronavirus-infected mouse models (8, 9), and a recently reported case of COVID-19-associated type I interferonopathy (10). In this respect, the timing of IFN 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 favourable clinical outcome. In contrast, late

administration (≥5 days after admission) is associated with increased in-hospital mortality, most likely due to an exacerbation of the cytokine storm associated with COVD-19 (11).

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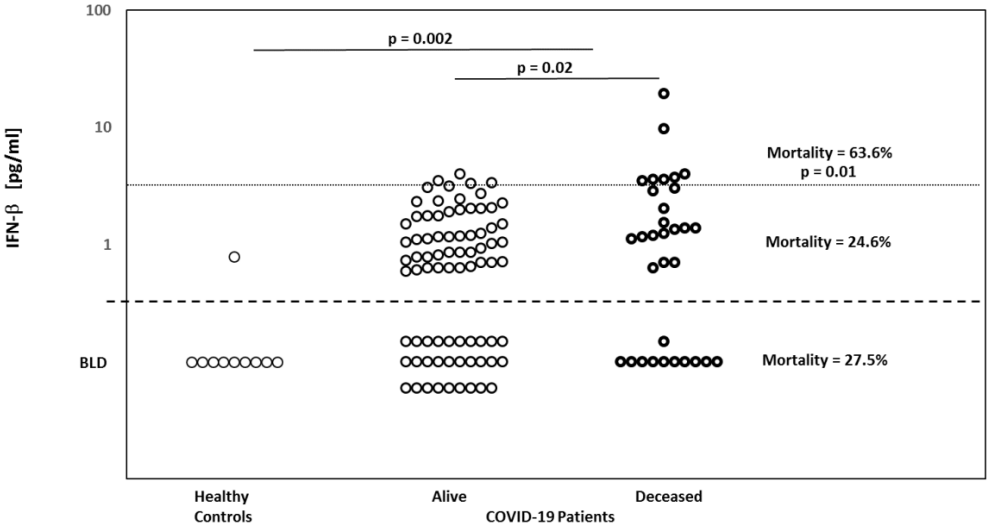

Figure 1: IFN-β levels among healthy controls and COVID-19 patients. Patients (N=112) presenting with a positive SARS-CoV-2 real-time reverse-transcriptase-polymerase-chain-reaction in their nasopharyngeal swab and pulmonary involvement were included at hospital admission. Mortality was assessed at day 30 after admission. Sampling time from onset of symptoms varied between 0 to 25 days (median 9). Healthy SARS-CoV-2-negative individuals (N=10) were included as controls. For all individuals, sera were stored less than 4 hours after collection at -80°C. Serum IFN-β levels were measured by highly sensitive ELISA (VeriKine-HS™ Human IFN-β ELISA Kit, PBL Assay Science, Piscataway, NJ, USA). Symbols represent individual patients. Dashed line represents limit of detection (0.59 pg/mL). Dotted line represents 90% percentile of IFN-β levels (3.4 pg/mL). P-value for COVID-19 mortality was calculated for patients with detectable IFN-β levels. Statistical significance of differences between groups was assessed using the non-parametric Mann-Whitney test and Fisher-exact test. The study was performed at the AP-HP Pitié-Salpêtrière Hospital in Paris and approved by the local ethical committee (#CER-SU-2020-21 and -31).

IFN: interferon; BLD: below limit of detection.