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Considering personalized Interferon- β therapy for COVID-19

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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 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 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.

References

1. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, Kazemzadeh H, Yekaninejad MS. 2020. A Randomized Clinical Trial of the Efficacy and Safety of Interferon beta-1a in Treatment of Severe COVID-19. *Antimicrob Agents Chemother* 64(9), e01061-20.
2. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, Gabbay FJ, Davies DE, Holgate ST, Ho LP, Clark T, Djukanovic R, Wilkinson TMA, Inhaled Interferon Beta C-SG. 2020. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* doi:10.1016/S2213-2600(20)30511-7.

3. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, Ng YY, Lo J, Chan J, Tam AR, Shum HP, Chan V, Wu AK, Sin KM, Leung WS, Law WL, Lung DC, Sin S, Yeung P, Yip CC, Zhang RR, Fung AY, Yan EY, Leung KH, Ip JD, Chu AW, Chan WM, Ng AC, Lee R, Fung K, Yeung A, Wu TC, Chan JW, Yan WW, Chan WM, Chan JF, Lie AK, Tsang OT, Cheng VC, Que TL, Lau CS, Chan KH, To KK, Yuen KY. 2020. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 395:1695-1704.
4. Arabi YM, Asiri AY, Assiri AM, Balkhy HH, Al Bshabshe A, Al Jeraisy M, Mandourah Y, Azzam MHA, Bin Eshaq AM, Al Johani S, Al Harbi S, Jokhdar HAA, Deeb AM, Memish ZA, Jose J, Ghazal S, Al Faraj S, Al Mekhlafi GA, Sherbeeni NM, Elzein FE, Al-Hameed F, Al Saedi A, Alharbi NK, Fowler RA, Hayden FG, Al-Dawood A, Abdelzaher M, Bajhmom W, AlMutairi BM, Hussein MA, Alothman A, Saudi Critical Care Trials G. 2020. Interferon Beta-1b and Lopinavir-Ritonavir for Middle East Respiratory Syndrome. *N Engl J Med* 383:1645-1656.
5. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Pere H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Pene F, Marin N, Roche N, Szwebel TA, Merkling SH, Treluyer JM, Veyer D, Mouthon L, Blanc C, Tharaux PL, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kerneis S, Terrier B. 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 369:718-724.
6. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B, Takahashi T, Tokuyama M, Lu P, Venkataraman A, Park A, Mohanty S, Wang H, Wyllie AL, Vogels CBF, Earnest R, Lapidus S, Ott IM, Moore AJ, Muenker MC, Fournier JB, Campbell M, Odio CD, Casanovas-Massana A, Yale IT, Herbst R, Shaw AC, Medzhitov R, Schulz WL, Grubaugh ND, Dela Cruz C, Farhadian S, Ko AI, Omer SB, Iwasaki A. 2020.

Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 584:463-469.

7. Lee JS, Park S, Jeong HW, Ahn JY, Choi SJ, Lee H, Choi B, Nam SK, Sa M, Kwon JS, Jeong SJ, Lee HK, Park SH, Park SH, Choi JY, Kim SH, Jung I, Shin EC. 2020. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci Immunol* 5(49) eabd1554.

8. Israelow B, Song E, Mao T, Lu P, Meir A, Liu F, Alfajaro MM, Wei J, Dong H, Homer RJ, Ring A, Wilen CB, Iwasaki A. 2020. Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling. *J Exp Med* 217(12): e20201241..

9. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. 2016. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe* 19:181-93.

10. Manzano GS, Woods JK, Amato AA. 2020. Covid-19-Associated Myopathy Caused by Type I Interferonopathy. *N Engl J Med* 383:2389-2390.

11. Wang N, Zhan Y, Zhu L, Hou Z, Liu F, Song P, Qiu F, Wang X, Zou X, Wan D, Qian X, Wang S, Guo Y, Yu H, Cui M, Tong G, Xu Y, Zheng Z, Lu Y, Hong P. 2020. Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients. *Cell Host Microbe* 28:455-464 e2.

12. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Beziat V, Manry J, Shaw E, Haljasmagi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de

Beek D, Roussel L, Vinh DC, Tangye SG, et al. 2020. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 370(6515), eabd4585.

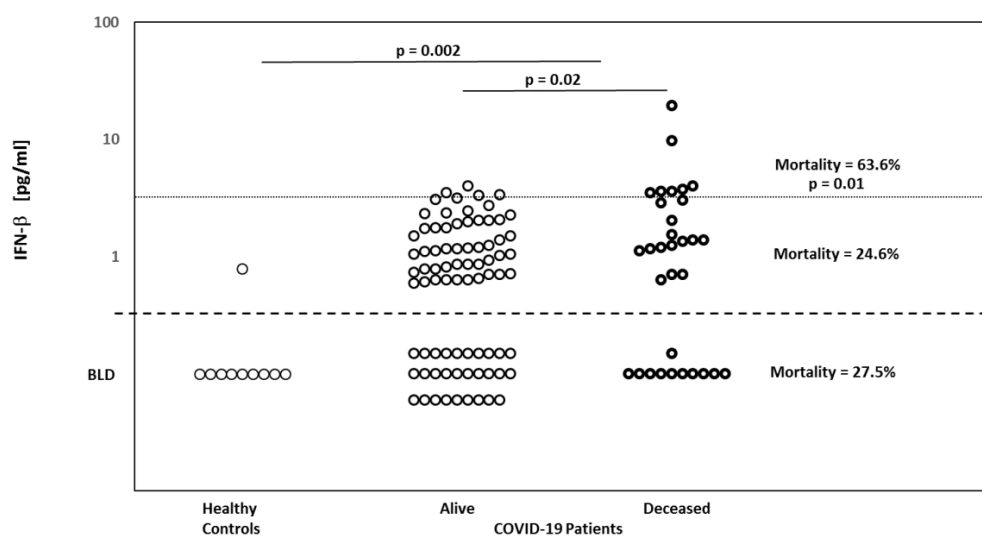


Figure 1: IFN- β levels among healthy controls and COVID-19 patients. Patients (N=112) presenting with a positive SARS-CoV-2 real-time reverse-transcriptase-polymerase-chain-reaction in their nasopharyngeal swab and pulmonary involvement were included at hospital admission. Mortality was assessed at 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.