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1 **Type I IFN immunoprofiling in COVID-19 patients**

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21

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43 Capsule summary:

44 COVID patients in ICU present a high mortality rate and immunoprofiling reveals heterogeneous IFN-
45 $\alpha 2$ production with about 20% of critically-ill patients unable to produce IFN- $\alpha 2$, highlighting the
46 immune response heterogeneity and opening avenues for targeted therapies.

47

48 To the editor,

49

50 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) is characterized
51 by a wide spectrum of disease encompassing asymptomatic carriage, mild to severe upper respiratory
52 tract illness that can evolve into respiratory failure or rapidly progressing severe viral pneumonia with
53 acute respiratory distress syndrome (ARDS). Disease severity depends on viral strain and host risk
54 factors have been identified such as age and male gender. In addition, an excessive immune response
55 has been identified in patients showing a cytokine storm associated with ARDS¹. Various
56 immunosuppressive drugs, including IL-6 blockers or JAK–STAT signaling inhibitors have been
57 suggested for the treatment of SARS-COV-2 infection² whereas additional clinical trials are evaluating
58 the use of recombinant interferon to foster host antiviral response. (Clinicaltrials NCT04315948,
59 NCT04293887). Type I interferons (IFN-I) are major components of the innate immune system and
60 represent critical antiviral molecules³. To date, IFN-I response has not been evaluated in COVID-19
61 patients and its contribution to the viral control and inflammation is unknown.

62 In this study, we assessed the kinetics of plasma IFN-I in COVID-19 patients with a spectrum of severity
63 degree. This study was approved by an ethical committee for biomedical research (Comité de
64 Protection des Personnes HCL). (Supplemental material and method of this article Online Repository).

65 Firstly, we explored three patients issued from the first COVID cluster diagnosed in France (Les
66 Contamines, Haute Savoie, France) in February 2020. We took advantage of the new digital ELISA
67 technology single-molecule arrays (Simoa)⁴ and analyzed the kinetics of plasma inflammatory
68 cytokines. Interleukin (IL)-6, C-reactive protein (CRP) and interferon γ -induced protein 10 (IP-10) were
69 elevated in the two symptomatic patients (Pt1, 3) (supplementary Figure 1 in the Online Repository).

70 Strikingly, no IFN- α 2 was detectable in these two patients. In contrast, IL-6, CRP and IP-10 remained
71 low during the hospital isolation stay for the asymptomatic individual and a significant elevation of

72 plasmatic IFN- α 2 was observed. Viral loads were low with no obvious quantitative difference between
73 all three patients.

74 We further explored a larger cohort of 26 critically ill COVID patients from one of the intensive care
75 unit (ICU) at Hospices Civils de Lyon (Lyon, France). Of note, all the patients were treated with standard
76 of care and none received antiviral or immunotherapies. Considering the first 28 days of infection,
77 more than half of critically ill patients required invasive mechanical ventilation (14/26). We observed
78 that patients demonstrated a peak in IFN- α 2 at day 8-10 of symptoms onset corresponding to the viral
79 replication phase, that decreased overtime to low but still detectable IFN- α 2 concentrations.
80 Conversely, a subset of patients (n=5, 19%) presented with sustained abrogation of IFN-I production
81 (Figure 1A). Simoa IFN α 2 measurement demonstrated a positive correlation with interferon-
82 stimulated genes (supplemental Figure 2A in this article's Online Repository) as already shown in viral
83 infections⁵. We noticed a strong pro-inflammatory response in all cases (CRP, IL-6 or IP-10), which
84 started early and remained positive while IFN-I response decrease after day 10 of infection (Figure 1B-
85 D). Patients with no IFN- α production presented poorer outcome, all of them requiring invasive
86 ventilation (n=5/5) and showing a longer ICU stay (Table 1). The viral load tended to be higher in IFN-
87 negative COVID-19 patients at disease diagnosis. IFN- β and IFN- λ were undetectable while low amount
88 of IFN- γ was detected in all patients with no evident link with IFN- α 2 level (supplemental Figure 2B-D
89 of this article's Online Repository).

90 Taken together, our data demonstrates a heterogeneous pattern of IFN- α response in COVID-19
91 patients with IFN-I response being impaired in about 1/5 of critically ill patients. This defective innate
92 immune response may be associated with a poor outcome. In murine models of SARS-CoV-1 infection,
93 delayed IFN-I production is associated with lung lesions and fatal outcome while early administration
94 of IFN-I prevents lung lesions⁶. SARS-CoV-2 displays a better sensitivity to IFN-I *in vitro* compared to
95 SARS-CoV-1 virus in infected cell lines⁷. Therefore, early administration of IFN- α 2 might be promising
96 for COVID-19 patients, especially in those who demonstrate a defective IFN response. The timing of

97 interferon exposition may be critical to control the virus and avoid immunopathogenesis.
98 Channappavanar et al. have shown that delayed IFN-I expression can be detrimental in mice in the
99 context of SARS-CoV-1 infection⁶. Our data suggests that screening patients for IFN production is
100 instrumental to select those who could benefit from early intervention with IFN. Following day 10, IL-
101 6 remains increased while IFN- α tapered. This kinetics highlight that cytokine inhibitors could be
102 helpful at the second phase of the disease following IFN-I decrease. Viral characteristic or individual
103 genetic susceptibility should be explored to understand the defect of IFN- α production in some COVID
104 patients. Some IFN- α 2 positive patients also experienced fatal outcome highlighting the multifactorial
105 causes of disease severity. We acknowledge limitations of this study, related to the small number of
106 included patients and the technical limitation for the measurement of IFN- β and IFN- λ , in this proof of
107 concept study.

108 Here, we provide new argues for an early intervention with recombinant IFN- α 2 and we also highlight
109 the window of opportunity for immunosuppressors at the second phase of the disease, opening new
110 avenues in COVID-19 therapies.

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Clinical features	Interferon negative (n=5)	Interferon positive (n=21)	P-value
Age (median [min-max])	81 [63-83]	74 [28-91]	0.696
Sex (male (%))	5 (100%)	18 (86%)	1.000
Delay between symptom onset and ICU admission (days)	7 [1-11]	7[0-15]	0.769
Bacterial co-infection during ICU stay (n (%))	3 (60%)	7(33%)	0.3402
Diabetes (n (%))	1 (20%)	3(14%)	0.5043
Chronic obstructive pulmonary disease (n (%))	0 (0%)	3(14%)	1.000
Cardiovascular disease (n (%))	2(40%)	9 (43%)	1.000
Hypertension (n (%))	3 (60%)	7 (33%)	0.3402
Cancer (n (%))	1 (20%)	3 (14%)	1.000
Active Smokers (n (%))	0 (0%)	1(5%)	1.000]
BMI>30 kg/m ²	3(60%)	8 (38%)	0.620
Biological features			
(median [min-max])			
Viral load at diagnosis (Ct)	20.9 [18-28.2]	25.1 [16.1-38.0]	0.172
Outcome			
Standard oxygen therapy only	0 (0%)	5 (24%)	0.5451
High flow oxygen therapy only	0 (0%)	7 (33%)	0.278
Invasive ventilation at any time during ICU stay	5 (100%)	9 (42%)	0.0425
ICU length of stay (median [min-max]) *	20 [7-30]	5 [0-35]	0.0503
Mortality at D28 after symptom onset(n(%))	2 (40%)	8 (38%)	1.000

CRP – C-Reactive Protein, ICU - Intensive Care Unit, BMI - Body Mass Index

130 **Table 1 - Clinical characteristics of COVID-19 patients in intensive care unit**

131 P-value are calculated using Mann-Whitney test for quantitative values and using Fisher-exact test for qualitative ones.

132 **Figure 1 – Plasma IFN- α 2 IL-6, CRP and IP-10 concentrations in COVID-19 critically ill patient cohort (n=26).**

133 A. Plasma Interferon (IFN)- α concentrations (fg/ml) were determined by single molecule array (Simoa). Fit Loess curve represent local polynomial regression
134 performed with Loess method, Confidence Interval at 95% was indicated (orange area).**A-D.** IL-6, CRP and IP-10 concentrations were measured using a
135 multiplexed assay with the Ella platform. Normal values for healthy volunteers was indicated by grey area. Vertical indicated median delay between symptom
136 onset and ICU admission.

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Figure 1

