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LETTER

Autoantibodies against type I interferons are associated with multi-organ failure in COVID-19 patients

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Dear Editor,

Neutralizing autoantibodies (auto-Abs) against type I interferons (IFN-I) have been identified as risk factor for life-threatening coronavirus disease 2019 (COVID-19) and were described in 101 of 987 (10%) patients with life-threatening pneumonia of whom 37 (37%) died [1]. In contrast, these antibodies were not found in patients with asymptomatic or mild disease and 0.33% of healthy individuals.

Auto-Abs against cytokines can cause severe or recurrent infections by neutralizing their target cytokine [2]. Auto-Abs to IFN-I without neutralizing ability in vitro have been identified in COVID-19 patients, but their clinical significance is unclear. Here we describe clinical characteristics of COVID-19 patients with auto-Abs neutralizing IFN-I, a subset of patients described by Bastard et al. [1]. In addition, we investigate the role of auto-Abs against IFN-I that were not neutralizing in vitro in COVID-19 and non-COVID-19 patients.

From 16 March 2020 to 8 June, 2020, 210 of 473 (43%) SARS-CoV-2 positive patients diagnosed by specific real time polymerase chain reaction (RT-PCR), hospitalized in Amsterdam UMC were selected based on sample availability and evaluated. As controls, 37 intensive care unit (ICU) patients were included who were admitted for other reasons than respiratory viral illness including COVID-19 (Supplemental Information). Clinical data were collected prospectively and blood samples were tested for auto-Abs against IFN- α2 and IFN-ω with a multiplex particle-based assay and ELISA. Blocking activity of auto-Abs was measured with a STAT1 phosphorylation assay.

Auto-Abs against IFN-I were found in 35 of 210 (17%) COVID-19 patients of whom 6 of 35 (17%) had neutralizing auto-Abs (Table 1). Neutralizing auto-Abs were only found in patients with severe COVID-19, all of whom required ICU admission compared to 83 of 204 (41%) of patients without neutralizing auto-Abs ($p=0.005$). Disease course was complicated by thromboembolic events in 3 of 6 patients (50%), acute kidney injury in 4 of 6 patients (67%) and superinfections in 4 of 6 patients (67%). Five of 6 patients (83%) died compared to 52 of 204 (26%) patients without neutralizing auto-Abs ($p=0.006$) including 35 of 83 (42%) in the ICU ($p=0.086$). All five patients with neutralizing auto-Abs died of COVID-19-induced multi-organ failure.

Auto-Abs without neutralizing ability in vitro were detected in 26 of 210 COVID-19 patients (12%). Presence of these auto-Abs had no effect on clinical course (Table 1; Supplementary Table 3). Auto-abs without neutralizing ability were present in 6 of 37 (16%) non-COVID-19 patients. The proportion of ICU patients with these auto-Abs was similar between COVID-19 and non-COVID-19 (12 of 89 [13%] vs. 6 of 37 [16%]; $p=0.78$).

Our study shows that auto-Abs against IFN-I that are not neutralizing in vitro occur frequently in ICU patients (16%), irrespective of COVID-19 infection. Auto-Abs

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Table 1 Baseline characteristics and clinical course of COVID-19 patients with neutralizing auto-Abs against IFN-I, with auto-Abs not neutralizing in vitro and without auto-Abs

	Patients with auto-Abs neutralizing in vitro (*N* = 6)	Patients with auto-Abs not neutralizing in vitro (*N* = 26)	Patients without auto-Abs (*N* = 175)
Age, years, median—IQR	69 (60–74)	61 (50–75)	64 (56–71)
Gender, male	6/6 (100%)	16/26 (62%)	111/175 (63%)
Comorbidities			
Hypertension	2/6 (33%)	14/26 (54%)	87/175 (50%)
Diabetes	1/6 (17%)	10/26 (39%)	51/175 (29%)
Obesity	1/6 (17%)	13/25 (50%)	61/169 (36%)
Complications			
Acute renal injury	4/6 (67%)	5/26 (19%)	15/175 (9%)
Bacterial pneumonia	2/6 (33%)	4/26 (15%)	20/175 (11%)
Thromboembolic event	4/6 67%)	4/26 (15%)	36/175 (21%)
Clinical course			
ICU admission	6/6 (100%)	12/26 (46%)	70/175 (40%)
Mortality	5/6 (83%)	8/26 (31%)	44/175 (25%)

that neutralize IFN-I were only found in severe COVID-19 patients and are associated with mortality. The cause of death was COVID-19-induced multi-organ failure in all, presumably attributed in part to inadequate IFN-I responses [3]. The antiviral immune response might be improved by therapies targeting neutralizing auto-Abs. As patients with non-neutralizing auto-Abs are not expected to benefit from such therapy, adequate patient selection is vital for future trials exploring auto-Abs targeted treatment.

Supplementary Information
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Authors contribution
The study was designed by JC, MB and DB. PB performed laboratory analysis. RK performed statistical analysis. The first draft of the manuscript was written by Rutger Koning and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Additional data are available upon request.

Code availability
Statistical code is available upon request.

Declarations

Conflicts of interest
The authors declare that they have no conflict of interest.

Ethics approval
Approval was obtained from the Medical Ethics Committees from the Academic Medical Center and VU University Medical Center.

Consent to participate/publication
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