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LETTER TO EDITOR

Autoantibodies Neutralizing Type I INFs May Be Associated with Efficacy of Tocilizumab in COVID-19 Pneumonia

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To the Editor:

IL-6 receptor blocker tocilizumab is one of the approved treatments of hypoxemic COVID-19 pneumonia. It is recommended by World Health Organization since July 2021 for treatment of patients with severe or critical COVID-19 infection. Nevertheless, contradictory studies about its efficacy underlined the difficulty to best define the target populations that would most benefit from this treatment [1, 2].

Recent studies reported the presence of pre-existing autoantibodies (auto-Abs) neutralizing type I interferons (IFNs) in at least 15% of patients with critical COVID-19 pneumonia. Moreover, these auto-Abs were found in almost 20% of deceased patients across all ages [3], being risk of death greater and age dependant [4] and indicating the importance of type I IFN immunity in host defense against SARS-CoV-2 infection. We aimed to assess the clinical impact of tocilizumab on mortality in patients with or without auto-Abs to type I IFNs in France, in the Seine-Saint-Denis department.

A cohort of 246 patients admitted for critical COVID-19 pneumonia was constituted in Robert Ballanger Hospital, Aulnay sous Bois, France, during the first wave of the pandemic. In this study, approved by a research ethics committee and registered on clinicaltrials.gov (NCT04366206), we assessed factors associated with clinical outcomes [2]. Critical COVID-19 pneumonia was defined by a pulse oxygen saturation (SpO_2) ≤ 96% despite oxygen support ≥ 6 L/min with oxygen mask, for more than 6 h [3]. Less than half (106/246) of these patients were treated by tocilizumab, with a mean time between first symptoms and treatment of 9.5 ± 4.6 days. We previously found that a single 400-mg dose was globally associated with improved survival without mechanical ventilation in patients with critical COVID-19 in our cohort [2].

In the same cohort of 246 patients, 139 patients were retrospectively selected because of an available serum sample that was collected during the acute phase of disease and tested for the presence of auto-Abs neutralizing type I IFNs [5]. A total of 7.9% (11 of 139) had circulating auto-Abs that neutralized 100 pg/mL IFN-α2 and/or IFN-ω (in plasma diluted 1/10) [5] (Fig. 1).

No differences were seen between patients with or without auto-Abs for comorbidities and biological characteristics at hospital admission. Although differences were not significant with the patients without neutralizing auto-Abs, most of patients with neutralizing auto-Abs were men (82%) and over the age of 65 years (82%) [5].

The presence of auto-Abs to type I IFNs was associated with an increased risk of mortality, as 6 of 11 (55%) patients with auto-Abs died versus 23 of 128 (18%) of patients without auto-Abs ($p = 0.01$). We previously reported that 6 of 29 (21%) patients who died of COVID-19 pneumonia in our entire cohort had circulating auto-Abs capable of neutralizing 100 pg/mL type I IFNs [5]. Deceased patients with auto-Abs did not present overt clinical differences with deceased patients without auto-Abs [5].

Six of the 11 patients (55%) with auto-Abs and 74 of the 128 patients (58%) without auto-Abs received tocilizumab ($p = 1$). Median time of administration after first symptoms did not differ between the two groups (8.5 [interquartile

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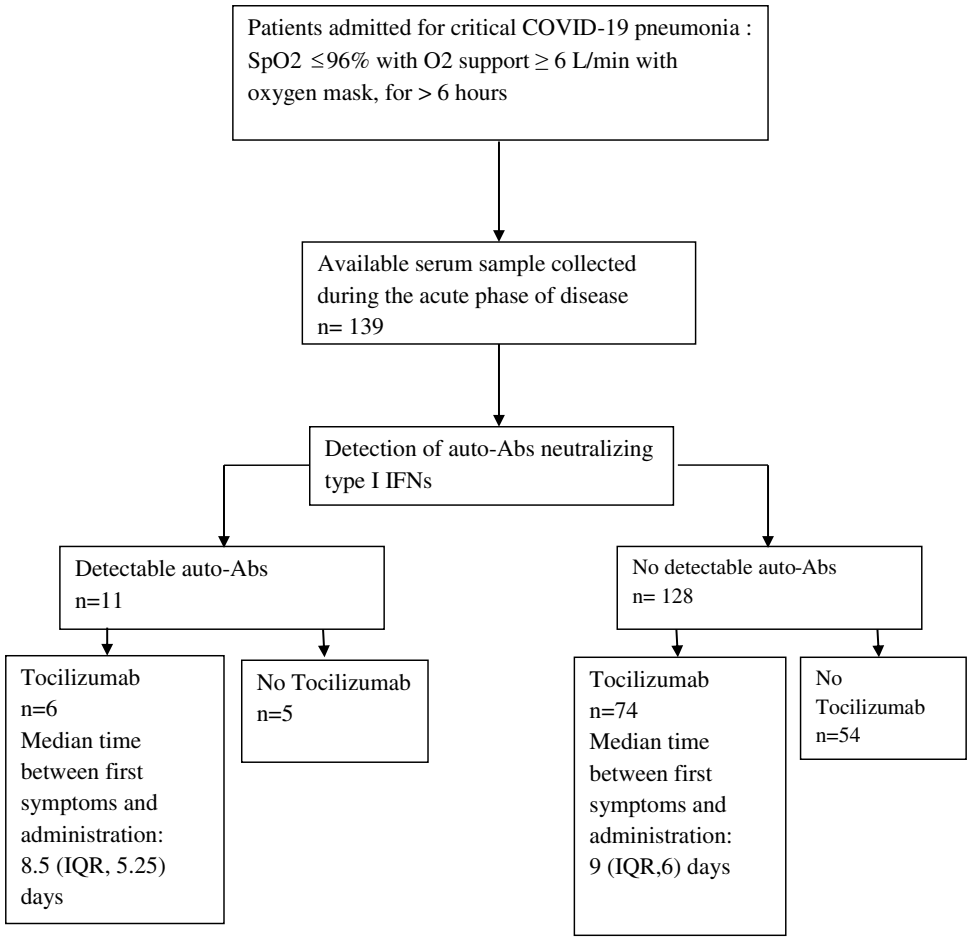

Fig. 1 Flow chart

range—IQR—5.25] days versus 9 [IQR, 6] days, $p = 0.7$) (Fig. 1).

Only 1 of 6 (17%) of deceased patients with neutralizing auto-Abs received tocilizumab versus 12 of 23 (52%) of deceased patients without auto-Abs, a difference that was not statistically significant ($p = 0.18$).

Interestingly, in patients with neutralizing auto-Abs, only 1 of 6 (17%) patients who received tocilizumab died versus 5 of 5 (100%) patients who did not received tocilizumab ($p = 0.01$). In contrast, in patients without neutralizing auto-Abs, 12 of 74 (16%) of patients who received tocilizumab died versus 11 of 54 (20%) patients who did not received tocilizumab ($p = 0.64$) (Table 1).

In patients with neutralizing auto-Abs who were not mechanically ventilated and whose oxygen support became < 6 L during hospitalization, there was no difference in the length of critical period (with oxygen support ≥ 6 L) between patients who received tocilizumab and patients who did not (Table 1).

In a surprising way, in patients without neutralizing auto-Abs and who were not intubated, length of critical period was significantly shorter in patients who did not received tocilizumab but increased in patients who received tocilizumab, without a significant effect on mortality or the need of invasive mechanical ventilation (Table 1). These results might suggest that tocilizumab would increase length of critical period in patients without neutralizing auto-Abs.

To note, very few patients were mechanically ventilated in our cohort that, as a reminder, was constituted during the first wave of the pandemic, with a limited number of places in intensive care unit. This may constitute a limitation to the interpretation of our results.

Overall, tocilizumab apparently showed somewhat better efficacy in reducing mortality in patients with than without neutralizing auto-Abs to type I IFNs in our study without evident beneficial effect on length of critical period.

It is important to highlight that the low number of patients with auto-Abs treated with tocilizumab is a significant limitation of this study and it will be necessary to confirm these results in larger cohorts. Meanwhile, the presence of auto-Abs to type I IFNs might be considered when selecting which patients should receive tocilizumab when suffering from hypoxemic COVID-19 pneumonia. It would also be interesting to compare the impact of other immunosuppressants and corticosteroids on mortality in patients with or without auto-Abs to type I IFNs.

Table 1 Effect of tocilizumab in patients with neutralizing auto-Abs to type I IFNs

	Patients with neutralizing auto-Abs ($n=11$)			Patients without neutralizing auto-Abs ($n=128$)		
	Tocilizumab $n=6$	No tocilizumab $n=5$	p	Tocilizumab $n=74$	No tocilizumab $n=54$	*p*
Poor outcome (invasive mechanical ventilation and/or death)	1 (17%)	5 (100%)	*0.01*	18 (24%)	20 (37%)	0.17
Invasive mechanical ventilation	0 (0%)	1 (20%)	0.45	10 (14%)	10 (19%)	0.47
Death	1 (17%)	5 (100%)	*0.01*	12 (16%)	11 (20%)	0.64
Delay between first symptoms and first poor outcome Median (IQR), days	14	16 (13)	NA	13 (4.75)	10.5 (7.75)	0.28
Length of critical period (O_2 support > 6 L) Median (IQR), days	10 (7)	12.5 (6.5)	0.69	6 (6.75)	3 (5.75)	*0.03*

Data are presented as a number (percentage) unless otherwise noted. Given the small samples size, a Fisher test was used to analyze the effect of dichotomous variables and a Mann–Whitney test for continuous variables. Significant values are noted in italics

NA not assessable

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Data Availability Clinical data files are stored at Robert Ballanger Hospital. It may be shared if needed.

Declarations

Ethics Approval This study was approved by a research ethics committee and was registered on clinicaltrials.gov (NCT04366206).

Consent to Participate Informed consent was obtained from the patients included in this study.

Consent for Publication The authors affirm that patients included in this study provided informed consent for publication.

Competing Interests JLC reports 2 patents pending, application number 63/055,155 filed July 22, 2020 and application number 63/141,669 filed January 26, 2021 pending.

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