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Coronavirus disease 2019 as a particular sepsis: a 2-week follow-up of standard immunological parameters in critically ill patients

Guillaume Monneret^{1*} , Martin Cour², Sébastien Viel³, Fabienne Venet¹ and Laurent Argaud²

Dear Editor,

Since the emergence of coronavirus disease 2019 (COVID-19), the number of patients admitted to ICU has never ceased to rise. While awaiting effective antiviral treatments, the understanding of the appropriate host immune response to a virus totally unknown of immune surveillance is of major importance. At the forefront of immune alterations previously described in COVID-19, patients homogeneously present severe lymphopenia [1, 2]. Interestingly, bacterial sepsis also deeply perturbs immune homeostasis by inducing a complex immune response that varies over time and associates a systemic inflammatory response and lymphopenia [3]. The objective of the present study was thus to conduct immune monitoring over the first 15 days in COVID-19 patients admitted to ICU based on markers previously evaluated in bacterial sepsis [4].

Thirty patients were included (supplemental methods and Table S1). After 2 weeks, 4 patients (13%) had died, 15 patients (50%) had left ICU and 11 (37%) still required mechanical ventilation. As previously reported, we observed a marked lymphopenia (Table 1) present upon admission and stable over the first 15 days. This affected all lymphocyte subsets as there was no alteration in lymphocyte subpopulation percentages or CD4/CD8 ratio (Table 1). Monocyte human leucocyte antigen–antigen D-related (mHLA-DR) expression was moderately

decreased upon admission and tended to diminish overtime down to around 9,000 AB/C. Lastly, cytokine levels were modestly elevated compared with results observed in bacterial septic shock. Of note, the most severe alterations were found in patients with acute respiratory distress syndrome (data not shown). Among the 4 patients who died by day 15, 2 presented very high IL-6 values (>7000 pg/mL) and 2 extremely low mHLA-DR (<4000 AB/C).

The present results shed light on immune response overtime in COVID-19 ICU patients. The majority of patients (86%) survived and presented with immune alterations that persisted at least during 2 weeks in patients still present in ICU. Overall, immune response to SARS-CoV-2 infection presents with similarities with the delayed step of immunosuppression in bacterial sepsis. These include (1) severe lymphopenia affecting all lymphocyte subsets, (2) decreased mHLA-DR but not as low as observed in bacterial septic shock and (3) moderately increased plasma cytokine levels showing at the same time both inflammatory (IL-6) and immunosuppressive (IL-10) responses. Accordingly, we report 30% of secondary infections (including one case of aspergillosis in an immunocompetent patient). Nevertheless, in COVID-19 patients, the remarkable stability of immune alterations overtime (dominated by the profound lymphopenia) is unusual in comparison with bacterial sepsis. We may hypothesize that the absence of potent antiviral drug along with immune defects could contribute to body's inability to normally eradicate virus and explain the long ICU stays reported by many authors. In agreement, a previous study showed negative correlation

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Table 1 Immunological parameters in 30 patients with COVID-19 over 2 weeks after ICU admission

	D0–D2 (n = 30)	D3–D5 (n = 20)	D6–D8 (n = 15)	D9–D10 (n = 11)	D11–D15 (n = 11)	Reference values
Ly count (cell/ μ L)	623 [478–907]	600 [440–866]	755 [395–935]	621 [294–1034]	684 [471–1160]	[1000 – 2800]
CD4 + T Ly count (cell/ μ L)	299 [192–393]	264 [202–398]	317 [218–439]	311 [117–534]	329 [210–662]	[336–1126]
CD4/CD8 Ly ratio	2.1 [1.6–2.8]	2 [1.5–2.8]	2.2 [1.9–3.3]	2.2 [2.1–3.3]	2.6 [2–3.4]	[1–4.9]
Monocyte HLA-DR (AB/C)	11,884 [8026–16,294]	10,012 [6285 – 16,696]	8436 [4927–15,245]	9074 [4748–16,731]	9509 [5107–26,068]	[13,500–45,000]
IL-6 (pg/mL)	68 [38–246]	120 [27–510]	95 [49–207]	71 [31–133]	80 [38–413]	< 7 pg/mL
IL-10 (pg/mL)	19 [11–32]	19 [7–32]	13 [8–25]	10 [6–16]	17 [8–30]	< 8 pg/mL
IL-6/IL-10 ratio	4.8 [0.9–10.3]	5.9 [1.9–12.3]	6.9 [3.3–14.8]	5.5 [4.3–8.5]	6.5 [4.5–13.6]	NA
CD4 + T Ly (% total Ly)	45 [37–52]	46 [35–50]	50 [39–55]	44 [40–51]	46 [42–54]	[33–62]
CD8 + T Ly (% total Ly)	23 [16–27]	22 [17–28]	21 [16–24]	22 [14–28]	21 [15–30]	[10–41]
B Ly (% total Ly)	12 [8–17]	18 [11–20]	18 [13–21]	18 [10–28]	12 [5–30]	[4–19]
NK Ly (% total Ly)	14 [8–18]	10 [8–13]	10 [5–13]	9 [6–12]	9 [5–13]	[5–33]

Cell phenotyping was performed by flow cytometry and cytokines measurement by Ella technology. Results are presented as median and [interquartile range]. References values are provided by routine clinical immunology laboratories at our institution. NA: not applicable

between lymphocytes count and pulmonary viral load [5].

By nature, this preliminary study presents with limitations (small size of the cohort, single center, incomplete immune profiling and no viral load follow-up during ICU stay). However, this provides additional information regarding immune response during COVID-19 after ICU admission and emphasizes the potential concern of a persistent immunosuppression that deserves attention in further studies.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-020-06123-1>) contains supplementary material, which is available to authorized users.

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Author contributions

SV, FV and GM performed immune measurements. MC and LA collected clinical data. All authors discussed the data, drafted or revised critically the manuscript for important intellectual content and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest

The authors declare they have no conflict of interest, including financial interests, activities, relationships and affiliations.

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