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Is IL-6 the Right Target in COVID-19 Severe Pneumonia?

To the Editor:

We read with great interest the article by McElvaney and colleagues, "Characterization of the Inflammatory Response to Severe COVID-19 Illness," published in the *Journal* (1). Systemic inflammation that characterizes acute respiratory distress syndrome (ARDS) in coronavirus disease (COVID-19) is associated with a high mortality rate (2). The term "cytokine storm" has emerged to explain the immunopathogenesis of most severe forms of COVID-19, because the release of many inflammatory cytokines (e.g., IL-6) was correlated with the disease severity (3). However, immune pathogenesis is still unsettled and comparisons with community-acquired pneumonia (CAP) from other origins are scarce. Interestingly, McElvaney and colleagues showed that COVID-19 cytokinemia is distinct, with circulating levels of IL-6 significantly higher in patients with COVID-19 than in those with non–COVID-19 severe CAP (1). These results are challenged by an editorial by Sinha and colleagues showing that plasma concentrations of IL-6 in patients with severe COVID-19 were lower than those observed in patients with ARDS from other origins (4). However, such comparisons are only possible if the respiratory severity is comparable between both groups.

We performed a prospective study that is part of the LYMPHONIE project (clinicaltrials.gov NCT03505281). We included non–immune-compromised patients with severe pneumonia (at least two criteria of the quick Sequential Organ Failure Assessment score and/or need for mechanical ventilation or vasopressors). Patients with COVID-19 all tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by RT-PCR. Plasma was collected within 48 hours of hospital admission and the concentration of IL-6 quantified using a Luminex assay (R&D Systems). Oral consent was obtained from the patient or their legal representatives. Approval was obtained from the ethics committee (Comité de Protection des Personnes Sud-MEDITERRANEE V) (2017-A03404-49).

Thirty-six patients without COVID-19 were enrolled between November 2018 and February 2020 (before the COVID-19 pandemic started in Burgundy, France) and 27 patients with COVID-19 in March and April 2020. Median age (interquartile range) was 67.5 (63–76.5) and 64 (57–71) in the non–COVID-19 and COVID-19 groups, respectively ($P = 0.0559$). ICU admission was needed for 32 (89%) and 27 (100%) patients of the non–COVID-19 and COVID-19 groups, respectively ($P = 0.07$). Pa_{O_2}:FI_{O_2} ratios were not different between groups (115.9 [74.6–157.9] vs. 145 [86–175.7] mm Hg, respectively; $P = 0.3073$). The IL-6 plasma concentrations were higher in the patients without COVID-19 than in those with COVID-19 (460.4 [138.2–4434.7] vs. 121 [75.7–236.6] pg/ml; $P = 0.0003$) (Figure 1).

Here, we showed that despite similar respiratory severity, plasma concentrations of IL-6 were dramatically lower in severe forms of COVID-19 than in CAP from other origins. Thus, although immune modulation is a promising therapeutic avenue that is likely to improve outcomes for COVID-19, the most relevant target and strategy remain to be found. ■

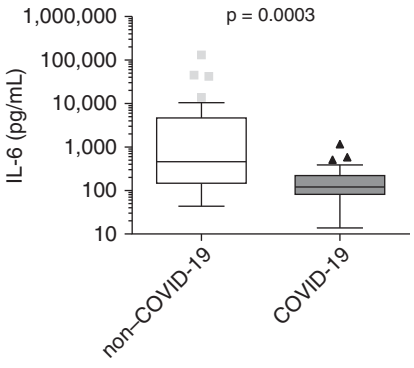

Figure 1. Box plot showing the plasma concentration of IL-6 within 48 hours of hospitalization in 36 patients with non–COVID-19 and 27 patients with COVID-19 severe pneumonia (LYMPHONIE study, 2018–2020). COVID-19 = coronavirus disease.

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Mathieu Blot, M.D., Ph.D.*
Infectious Diseases Department University Hospital
Dijon, France
and
LNC INSERM UMR1231
Dijon, France

Abderrahmane Bourredjem, M.Eng., M.Sc.
INSERM CIC1432 Clinical Epidemiology unit
Dijon, France

Christine Binquet, M.D., Ph.D.
LNC INSERM UMR1231
Dijon, France
and
INSERM CIC1432 Clinical Epidemiology unit
Dijon, France

Lionel Piroth, M.D., Ph.D.
Infectious Diseases Department University Hospital
Dijon, France
and
INSERM CIC1432 Clinical Epidemiology unit
Dijon, France

On behalf of the LYMPHONIE Study Group

ORCID ID: 0000-0001-6541-2434 (M.B.).

*Corresponding author (e-mail: mathieu.blot@chu-dijon.fr).

LYMPHONIE Study Group: Mathieu Blot, Abderrahmane Bourredjem, Christine Binquet, Lionel Piroth, Jean-Pierre Quenot, Pierre-Emmanuel Charles, François Aptel, Sébastien Prin, Pascal Andreu, Marie Labruyère, Auguste Dargent, Maxime Nguyen, Belaid Bouhemad, Marjolaine Georges, Philippe Bonniaud, Guillaume Beltramo, Marielle Buisson, Bernard Bonnotte, Philip Bielefeld, Jeremy Barben, Alain Putot, Serge Monier, Audrey Large, Suzanne Mouries-Martin, Hervé Devilliers, Pascal Chavanet, and Alexandre Guilhem.

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Role of IL-6 in Severe Inflammation

To the Editor:

We read with interest the recent article investigating coronavirus disease (COVID-19) inflammatory cytokine profiles by McElvaney and colleagues, in which, in critically ill patients requiring intensive care, circulatory IL-6 was elevated (1), as recent reports have indicated this cytokine as the strongest predictor of the need for mechanical ventilation (2). However, we would like to raise a potential problem with the authors' interpretation of the results before discussing the application to IL-6–regulating medicines, as we think that it is not clear that IL-6 is a key molecule of severe inflammation like other proinflammatory cytokines, such as tumor necrosis factor and IL-1. There are several reports advocating both the proinflammatory and antiinflammatory potential of IL-6 against acute inflammatory responses, including acute respiratory distress syndrome and sepsis (3, 4). Using genetically engineered animals (IL-6–deficient B6J129Sv mouse strain), we previously demonstrated that IL-6 serves as a protector in pulmonary hemorrhagic injury induced by bacterial endotoxins (LPS), at least partly through the regulation of proinflammatory cytokines and chemokines (5). However, in this study, interestingly, we also observed that IL-$6^{-/-}$ mice show devastating lung injury compared with littermate wild-type mice 3 days after intraperitoneal administration of LPS, whereas mortality at Day 7 was higher in wild-type than in IL-$6^{-/-}$ mice (repeated three times; K. Inoue and colleagues, unpublished data), suggesting that IL-6 can have opposite effects depending on the pathological phase of the host. We imagine that IL-6 has multiple roles in the inflammatory pathway, as proposed by Qiu and colleagues (6), although the role may differ according to animal species and strain and inflammation type. Indeed, we have confirmed that this cytokine is not valuable in acute oxidative lung injury induced by diesel exhaust particles in mice with the same genetic background as in the LPS experiments.

Further research is needed to clarify the role of IL-6 in severe inflammatory conditions, including COVID-19–related conditions, and explore novel therapeutic options. ■

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Ken-ichiro Inoue, M.D., Ph.D.*
University of Shizuoka
Shizuoka, Japan

Tomoya Sagawa, M.D.
Hirohisa Takano, M.D., Ph.D.
Kyoto University
Katsura, Kyoto, Japan

ORCID IDs: 0000-0002-9723-5847 (K.-i.I.); 0000-0003-3048-0319 (T.S.).

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