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Reply to Blot *et al.* and to Inoue *et al.*

From the Authors:

We thank Blot and colleagues for their interest in our article and for raising an important question regarding the suitability of IL-6 as a therapeutic target in coronavirus disease (COVID-19).

In their correspondence, Blot and colleagues provide data on IL-6 levels measured in patients with a diagnosis of COVID-19 versus non-COVID-19 pneumonia. Although we believe the data presented by Blot and colleagues are valid, we suggest that the IL-6 levels depicted are, by virtue of sample timing, processing methodology, and patient severity of disease, not comparable to ours and should be interpreted in context.

In the study conducted by Blot and colleagues, patients were sampled during the first 48 hours of their hospital admission, following confirmation of their diagnosis by RT-PCR. In contrast, our patients were matched for time from onset of symptoms (1). Had we not taken this approach, we risked confounding our data by sampling patients who had the same disease severity but who

were merely at different points in the course of their illnesses. Moreover, the criteria for admission and the availability of testing, both locally and internationally, have shifted repeatedly throughout the current pandemic, making comparisons between studies that use admission as a starting point challenging. COVID-19 is widely regarded as a biphasic illness (2), with a later “hyperinflammatory phase” occurring 7 days from the onset of symptoms.

Blot and colleagues matched patients for disease severity by using the Pa_{O₂}:Fi_{O₂} ratio. However, the Pa_{O₂}:Fi_{O₂} readings and blood sampling were performed at different time points in the patient’s hospital stay, with approximately three-quarters of the Pa_{O₂}:Fi_{O₂} ratios for the COVID-19 group calculated later, after these individuals had progressed to the ICU. In our study, blood and physiological measurements were performed simultaneously. In addition, all of our patients with COVID-19 were receiving invasive mechanical ventilation, whereas 15% of the COVID-19 ICU group described by Blot and colleagues were not. Mechanical ventilation influences the Pa_{O₂}:Fi_{O₂} ratio, such that patients who are not receiving invasive ventilation have lower Pa_{O₂}:Fi_{O₂} ratios and appear sicker than patients who are ventilated with high levels of positive end-expiratory pressure and optimal lung recruitment.

The effects of sample timing and severity of illness are crucial when cytokine levels are being assessed. To illustrate this point, the mean daily difference in IL-6 levels for the COVID-19 group described by Blot and colleagues ranged from 10,000 to 14,000 pg/ml.

The study protocol used by Blot and colleagues allowed up to 4 hours to elapse before samples underwent initial processing. This delay is relevant, as IL-6 and other cytokines are released spontaneously from blood cells over time (3, 4). In contrast, our samples were processed immediately using protective centrifugation speeds without temperature shifts.

Unlike our study, Blot and colleagues did not match for markers of severity of inflammation, such as C-reactive protein, nor did they account for the diurnal variation in circulating IL-6 levels by standardizing their time of sample collection. Additionally, a large number of the patients with COVID-19 included by Blot and colleagues were already receiving therapies such as corticosteroids that are known to influence cytokine levels. In our study, these patients were excluded.

The non-COVID-19 severe community-acquired pneumonia (CAP) group recruited by Blot and colleagues was also different from ours, with a predominance of atypical pathogens. Indeed, *Streptococcus pneumoniae*, the most common CAP pathogen, was detected in only 2 of the 36 patients with non-COVID-19 severe CAP described. Furthermore, four of the severe CAP group in the Blot study had positive bacterial blood cultures. Patients with bacteremia and/or septicemia were excluded from our study because of their high likelihood of generating outlier levels of blood cytokines.

These factors may go some way in explaining the degree of variation in the IL-6 levels reported by Blot and colleagues. The greater than 1,000-fold difference in IL-6 levels within their non-COVID-19 pneumonia group is still unusual, however, and levels approaching or in excess of 100,000 pg/ml in several patients would prompt consideration of alternative or concomitant diagnoses.

We agree strongly with Inoue and colleagues that blanket inhibition of IL-6 in COVID-19 should be approached with caution given the complex biology of this cytokine.

To achieve signal transduction, IL-6 first binds IL-6R (IL-6 receptor, a cell surface receptor). After this binding event, the IL-6/IL-

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6R complex associates with a second protein, gp130 (5, 6). Signaling via membrane-bound IL-6R is termed classic signaling. Though gp130 is present in all cells, IL-6R is only expressed by a select few, most notably hepatocytes and macrophages. Therefore, only certain cells are IL-6 responsive under usual circumstances.

However, during acute inflammatory states, IL-6R is cleaved by ADAM-17, creating a soluble receptor, sIL-6R, which is capable of binding IL-6. The IL-6/sIL-6R complexes that subsequently form are capable of binding gp130. This process, known as trans-signaling, thereby enables cells that do not express IL-6R to become IL-6 responsive.

Critically, the antiinflammatory and antibacterial activities of IL-6 are mediated via classical signaling, whereas the proinflammatory activities of IL-6 are mediated by trans-signaling (5, 6). This is important, as monoclonal antibodies against IL-6R do not discriminate between classical or trans but instead block both types of IL-6R signaling. This is the rationale for increased bacterial infection in patients treated with tocilizumab. IL-6 is also necessary for resolution of H1N1 influenza infection by protecting neutrophils from virus-induced death in the lung and by promoting neutrophil-mediated viral clearance (7).

In addition to pathogen clearance, the acute phase proteins such as α -1 antitrypsin (AAT) are also induced via classical IL-6 signaling. A treatment that ablates the AAT response altogether would seem risky. Tocilizumab cannot be reversed once administered and has a terminal half-life of approximately 21.5 days. Furthermore, the safest way to wean patients with COVID-19 from this therapy has yet to be agreed upon. We believe that treatment aimed at changing the level or activity of a specific cytokine such as IL-6 may represent a double-edged sword and that therapeutic approaches that address the underlying cause of changes in IL-6 and other mediators are more likely to be successful. In the event that inhibition of the inflammation driven by IL-6 alone is required, specific blockade of IL-6 trans-signaling would preserve cytokine balance and bacterial clearance and might therefore be a superior strategy. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Respiratory Drive Measurements Do Not Signify Conjectural Patient Self-inflicted Lung Injury



To the Editor:

We read with interest the editorial by Gattinoni and colleagues on the role of respiratory drive in the application of mechanical ventilation in patients with coronavirus disease (COVID-19) (1).

Gattinoni and colleagues conclude that measurements of airway occlusion pressure ($P_{0.1}$) and maximal deflection in airway pressure during end-expiratory airway occlusion (ΔP_{occl}) “displayed good prognostic performance in predicting respiratory deterioration at 24 hours” and can forewarn against patient self-inflicted lung injury (P-SILI).

Apart from the arbitrary definition of respiratory deterioration, the scatter plot in Figure 1 of the article by Esnault and colleagues (2) shows that the vast majority of data overlap between the two groups: 66% of $P_{0.1}$ values in nine “Relapse” patients overlap with 74% of $P_{0.1}$ values in 19 “Non-Relapse” patients. Only one value of ΔP_{occl} in the “Relapse” group does not overlap with values in the “Non-Relapse” group. Gattinoni and colleagues fail to point out that the “break-points” were

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