Targeting IL-1, IL-6 or GM-CSF in COVID-19. Response to: 'More evidences on which biologic and which pathway is key in severe-critical COVID-19 pneumonia' by Ferraccioli

We thank Prof Ferraccioli for his positive comments on our open-label trials with sarilumab, tocilizumab, anakinra and mavrilimumab in patients with severe hyperinflamed COVID-19[1–4] and for remarking the unprecedented opportunity offered by our studies to better understand the relative contribution of different targetable inflammatory pathways to the pathogenesis of severe COVID-19.[5] The study designs we adopted should be definitely interpreted in light of the scientific data that progressively became available and of the course of the pandemic wave that struck Northern Italy and our Institution. Between 24 February and 22 May 2020, San Raffaele Hospital (Milan, Italy) admitted more than 1000 patients with COVID-19.[6–8] Intriguingly, the clinical phenotype of admitted patients changed over time and the severity of the disease progressively varied in parallel with outbreak exhaustion.[6]

When our hospital was first hit by the pandemic, accumulating evidence from China was pointing at interleukin (IL)-6 as a master regulator of the cytokine storm occurring in severe COVID-19.[9] Tocilizumab was, therefore, first used as a potential treatment[2] and subsequently replaced by intravenous sarilumab due to sudden shortage of the drug.[1] As described in our studies, however, none of the two IL-6 receptor antagonists convincingly impacted disease outcomes, prompting the search for alternative therapeutic strategies.[1 2] Blockade of IL-1 and of granulocyte–macrophage colony-stimulating factor (GM-CSF) was deemed potential rational approaches based on the upstream position of these molecules in the inflammatory cascade and on the ready availability of selective inhibitors.[9 10] In particular, due to its remarkable safety profile, intravenous anakinra was administered mainly to patients affected by severe acute respiratory distress syndrome managed outside intensive care unit (baseline Pao_2:Fi_{o2} <100 mm Hg in 86% of cases).[3] On the contrary, mavrilimumab was administered at later stages of the COVID-19 outbreak when admitted patients were generally less compromised (baseline Pao_2:Fio_2 >100 mm Hg in 92% of cases).[4] Hence, because our studies were not conducted in parallel and patients enrolled largely differed in terms of age and severity, mortality rates were also different among the four groups of matched controls treated with standard of care. Accordingly, although an oversimplistic comparison between the weighted mortality rate of patients treated with standard of care (30%) and with anticytokine therapies (10%) would suggest better outcomes in the latter group, our studies were not designed to clarify the relative efficacy of each single biologic agent.[1–4] The dilemma of whether to preferentially target IL-1, IL-6 or GM-CSF in severe COVID-19 remains, therefore, to be solved.

Yet, our pioneering experience returned three major pathophysiological insights. First, mechanisms inherent to IL-6 pathway are likely not the only drivers of severe COVID-19 as serum IL-6 levels were not associated with disease mortality, lung consolidation or respiratory failure in our patients.[1 6] Accordingly, IL-6 blocking strategies with either tocilizumab or sarilumab were not associated with clinical improvement in patients with critical COVID-19 compared with local standard of care.[1 6] Further evidence of the apparent inefficacy of anti-IL-6 treatments in severe disease is, indeed, provided by the early termination of a phase 3 randomised-controlled trial of intravenous sarilumab 400 mg conducted in the USA: in this trial involving 194 patients with severe COVID-19 sarilumab did not provide any additional benefit compared with placebo in mechanically ventilated patients and was associated with a negative trend in not mechanically ventilated subjects.[11]

Second, targeting IL-1 or GM-CSF seems a more promising approach since upstream blockade of the inflammatory cascade may allow a better control of cytokine storm-induced organ damage with a better safety profile. Third, the sarilumab study revealed for the first time that the degree of lung consolidation predicted disease response to a biologic treatment, a finding that may be of relevance for designing further clinical trials.[1] In this sense, intercepting rampant inflammation before the establishment of lung damage remains imperative to avoid COVID-19 progression to stages where even biologic agents might not be effective. Indeed, preliminary evidence of the effective early administration of anti-inflammatory molecules targeting the inflammasome activation such as colchicine seems to support the rationale of this approach.[12]

The results of ongoing randomised placebo-controlled trials comparing IL-1 and IL-6 blocking strategies on larger number of patients with COVID-19 are eagerly awaited to possibly substantiate our observations and to definitively rank the efficacy of different anticytokine therapies.[13] A retrospective comparison of our entire cohort of patients treated with standard of care versus each single biologic agent is also currently under preparation and will be based on a rigorous case–control matching in order to contain analytical biases and to retrieve informative results.

Emanuel Della-Torre [1,2] **Corrado Campochiaro** [1,2] **Giulio Cavalli**,[1,2] **Giacomo De Luca**,[1,2] **Fabio Ciceri**,[2,3] **Alberto Zangrillo**,[2,4] **Lorenzo Dagna** [1,2]

[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), San Raffaele Scientific Institute, Milan, Italy
[2]Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milan, Italy
[3]Hematology and Bone Marrow Transplant Unit, San Raffaele Scientific Institute, Milan, Italy
[4]Department of Anesthesia and Intensive Care, San Raffele Scientific Institute, Milan, Italy

Correspondence to Dr Emanuel Della-Torre, Università Vita-Salute San Raffaele, San Raffaele Scientific Institute, Milan 20132, Italy; dellatorre.emanuel@hsr.it

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ORCID iDs
Emanuel Della-Torre http://orcid.org/0000-0002-9192-4270
Corrado Campochiaro http://orcid.org/0000-0001-6806-3794
Lorenzo Dagna http://orcid.org/0000-0002-7428-315X

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