Impact of sarilumab on mechanical ventilation in patients with COVID-19. Response to: 'Correspondence on: 'Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation–an open-label cohort study' by Della-Torre *et al*' by Cheng and Zhang

We thank Dr Zhang and colleagues for appreciating our work and for raising relevant comments on the use of non-invasive ventilation (NIV) and mechanical ventilation (MV) in our population of critical patients.[1] The authors correctly noticed that the vast majority of patients (52/58, 93%) fulfilled the criteria for acute respiratory distress syndrome (ARDS) but they did not undergo MV or glucocorticoids as per the 'Surviving Sepsis Campaign Guidelines for Critically Ill Adults with COVID-19'.[2 3] Indeed, the standard therapeutic approach adopted in our institution during the pandemic wave that struck Northern Italy varied in light of the practical experience that we rapidly accumulated and of the scientific data that progressively became available.

Between 24 February and 22 May 2020, San Raffaele Hospital (Milan, Italy) admitted more than 1000 patients with COVID-19, and our study was carried out in March, when shortcomings of MV in this specific clinical setting were increasingly being reported.[4 5] Mounting evidence on invasively ventilated patients with COVID-19, in fact, was pointing at an extremely high mortality rate, ranging from 86% to 97%, and available guidelines at that time were not recommending early MV in case of ARDS.[3 6 7] We therefore applied continuous positive airway pressure (CPAP) whenever possible outside intensive care units (ICUs) based on its established efficacy in patients with hypoxaemia and on our historical positive experience with this approach.[8–10] In particular, 13 (23%) patients in our cohort ultimately required intubation and MV in ICU, while the remaining patients were managed outside the ICU, either with high-flow oxygen support or with NIV, some of them with pronation.[11] CPAP (positive end-expiratory pressure=10 cm H_2O, FiO_2=0.6) was introduced when oxygen saturation was <94% despite high-flow oxygen therapy, starting with four daily cycles of 3 hours each and then personalised according to the patient's need. At baseline, no patient had cardiogenic pulmonary oedema or altered state of consciousness. The mean peripheral oxygen saturation was 94% (±3.3), and the mean PaO_2 on arterial blood gas was 75 mm Hg (±13.5), with all patients being on respiratory distress while not on oxygen support. No patients reported hypotension either before or after NIV, and none required vasoactive drugs during follow-up observation outside the ICU. MV-free survival at 28 days was similar between patients treated with sarilumab and with standard of care, with a median time to MV of 5 and 3 days, respectively.[1]

Dr Zhang and colleagues also asked about the use of glucocorticoids in our cohort. Indeed, a recent observational Dutch study reported that a short course of high-dose methylprednisolone alone or combined with anti-interleukin (IL)-6 treatment improved survival and reduced the need for MV in hospitalised patients with COVID-19 compared with a retrospective cohort of subjects treated with standard of care.[12] Yet, significantly higher body mass index, incidence of diabetes and requirement of MV at baseline were observed in controls, introducing a major bias in patient selection and outcome interpretation.[12] As far as our experience is concerned, at the time when we conducted our study, clinical evidence did not univocally support corticosteroid treatment for COVID-19-associated pneumonia.[13] As opposed to septic shock, in fact, shock during severe hypoxaemic respiratory failure is often a consequence of increased intrathoracic pressure (during invasive ventilation) impeding cardiac filling, a context where steroid treatment is unlikely to provide a benefit.[13] In addition, available observational data from influenza, SARS-CoV and Middle East respiratory syndrome coronavirus infections suggested increased mortality, impaired viral clearance and complications of corticosteroid therapy in survivors, further arguing against the use of glucocorticoids in critical COVID-19.[13] Considering the aforementioned data, also currently available guidelines recommend against the routine use of systemic corticosteroids for respiratory failure in patients with COVID-19.[3]

This last observation—namely, the lack of efficacy of anti-inflammatory therapy with glucocorticoid in advanced stages of COVID-19—is, indeed, in agreement with the disappointing results obtained in our study as well as in randomised controlled trials with IL-6 blocking agents in patients with severe hyperinflamed COVID-19 pneumonia (http://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00; https://www.roche.com/investors/updates/inv-update-2020-07-29.htm).[1 14] More recent evidence seem to indicate that other immunosuppressive agents might be more effective in this setting and that early administration of anti-inflammatory molecules, such as colchicine or even steroids, might represent the optimal strategy to intercept rampant inflammation before the establishment of irreversible lung damage in COVID-19.[15–17] While awaiting for definitive confirmation by ongoing randomised controlled trials, early domiciliary treatment with anti-inflammatory therapies might be of great help to COVID-19 epidemic areas, particularly those facing a shortage of medical devices, such as South American countries, South Africa and India.

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