Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease

To the Editor:

Recent evidence derived from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), shows a direct correlation between the severity of systemic inflammation, progression to respiratory failure, and fatal outcome.1 The appearance of clinical signs of severe pneumonia is associated with progressive and persistent elevation of D-dimer and inflammatory markers, including ferritin, a laboratory biomarker of macrophage activation.1 These findings are consistent with the characteristics of the immunological infiltrate described in lungs infected with SARS-CoV-2, which is marked by diffuse macrophage infiltration and is consistent with cytokine overproduction.2,3 These features are reminiscent of syndromes characterized by overt inflammation driven by the release of proinflammatory cytokines, such as macrophage activation syndrome and Still’s disease, which suggests that an early anti-inflammatory approach in patients who develop interstitial pneumonia could be crucial to prevent the progression of lung damage toward respiratory failure requiring ventilatory support and ultimately death.4

The IL-6 blocker tocilizumab, administered with the same protocol used in cytokine release syndrome secondary to chimeric antigen receptor-T therapies, has provided encouraging preliminary results.5 These results support the use of anti-inflammatory treatments in the management of COVID-19–related pneumonia. The potential effectiveness of glucocorticoid therapy, although controversial, has been recently highlighted in patients with acute respiratory distress syndrome.6

The rapid expansion of the pandemic in Italy in the past weeks has led to a shortage of tocilizumab, thus prompting the search for alternative therapeutic strategies based on other cytokine blockers. Recent studies have shown that coronavirus regulates the activation of NLRP3 inflammasome by inducing the maturation and secretion of IL-1β,7 suggesting a potential role for IL-1 inhibitors in the management of the inflammatory complications induced by SARS-CoV-2.

Here, we report the first experience with the early use of high intravenous (IV) doses of the recombinant IL-1 receptor antagonist (anakinra) in 5 patients with severe/moderate COVID-19 with pulmonary involvement. The rationale for the use of anakinra at high IV doses, rather than at the standard regimen of 100 mg/daily subcutaneously, derives from previous experiences in other conditions characterized by massive cytokine release, such as severe secondary hemophagocytic lymphohistiocytosis8 and sepsis.

On admission, all patients displayed a recent onset of dyspnea, associated with fever, systemic inflammation, rapidly worsening respiratory distress, and marked lung abnormalities on chest computed tomography (Table I; Fig 1, A-C). Soon after admission, all patients received, after providing informed consent, treatment with high-dose IV anakinra added to the current standard of care (Table I). The starting dose was 100 mg every 8 hours (300 mg/daily) for 24 to 48 hours, followed by tapering, according to clinical response. Methylprednisolone was also administered in patient 4 (Table I). The off-label use of anakinra was approved by the internal review board of the Galliera Hospital.

All 5 patients experienced rapid resolution of systemic inflammation, and remarkable improvement in respiratory parameters, with reduction of oxygen support requirement and early amelioration of chest computed tomography scan abnormalities before discharge in 3 patients (Table I; Fig 1, A-C). All patients were discharged 6 to 13 days after the start of anakinra. No secondary infections or other adverse events were observed.

These results compare favorably with literature data, showing that patients with a similar inflammatory phenotype and severe respiratory impairment have a high risk for a lethal outcome.1 Our decision to use anakinra was motivated by the shortage of tocilizumab and by the high mortality rate previously observed in our center among patients with prominent inflammatory features and marked respiratory distress. In our preliminary experience, the addition of high-dose IV anakinra to the standard of care enabled rapid control of the inflammatory manifestations and led to a favorable outcome.
We acknowledge the limitations related to the noncontrolled nature of our study, the small size of the patient population, the short-term duration of the treatment, and the variability in laboratory biomarkers. However, these preliminary findings suggest the potential safety of an early anti-inflammatory treatment with high doses of IV anakinra, in the cytokine release syndrome occurring in patients with COVID-19. We propose, therefore, to add anakinra to the list of possible anticytokine treatments for COVID-19–related pneumonia. 6 The ultimate assessment of the efficacy and safety of anakinra therapy in COVID-19 pneumonia should be conducted in the context of randomized clinical trials. In this line, an open-label trial based on the administration of 400 mg daily of IV anakinra for 14 days has just started patient recruitment in Italy (NCT04324021) and will provide further evidence. In our preliminary experience, even lower doses of IV anakinra and shorter treatment duration provided a favorable outcome, without significant side effects, in particular secondary infections.

Emanuele Pontali, MD* Stefano Volpi, MD, PhD* Giancarlo Antonucci, MD* Marco Castellaneta, MD Davide Buzzi, MD Francesca Calautti, Pharm D Elio Castagnola, MD Gian Andrea Rollandi, MD Angelo Ravelli, MD Giovanni Cassola, MD* Marco Gattorno, MD*

TABLE I. Clinical characteristics of patients at hospital admission, therapeutic interventions, and outcome

| Characteristic | P1 | P2 | P3 | P4 | P5 |
|---------------|----|----|----|----|----|
| Age (y)       | 62 | 59 | 40 | 55 | 56 |
| Sex           | M  | M  | F  | F  | M  |
| Comorbidities | Cardiovascular disease, hyperlipidemia | — | — | Cardiovascular isease, hypertension | — |

| Emergency department presentation | P1 | P2 | P3 | P4 | P5 |
|-----------------------------------|----|----|----|----|----|
| **SARS-CoV-2 nasal swab** | Positive | Positive | Positive | Positive | Positive |
| Anakinra administration | Days after disease onset | 10 | 9 | 6 | 5 |
| | Days after admission | 2 | 3 | 0 | 1 |
| | Cumulative dose (mg) | 600 | 1400 | 900 | 1000 |
| Other therapies administered | | | | | |
| | HCQ, enoxaparin, antiviral, azithromycin | | | | |
| | HCQ, enoxaparin, antiviral, azithromycin | | | | |
| | HCQ, enoxaparin, antiviral, azithromycin | | | | |
| | MPred (0.5-1 mg/kg/d for 3 d), enoxaparin, azithromycin | | | | |

| Results | P1 | P2 | P3 | P4 | P5 |
|---------|----|----|----|----|----|
| Days of CPAP (PEEP 10 cm H₂O) | FiO₂ 35%-60% (Venturi mask) | — | 13 | — | 3 |
| FiO₂ 24%-32% (nasal cannula) | Ambient air | — | 3 | 1 | 4 |
| Hospitalization | Hospitalization after anakinra | 16 | 13 | 14 | 10 |

| Parameter | Range | P1 | P2 | P3 | P4 | P5 |
|-----------|-------|----|----|----|----|----|
| PaO₂/FiO₂ | 37.7 | 38.2 | 37.6 | 37 | 37.1 |
| Temperature (°C) | 38.2 | 97% | 38.2 | 97% | 37.6 | 94% | 37 | 97% | 37.1 | 85% |
| °C | 38.2 | 97% | 38.2 | 97% | 37.6 | 94% | 37 | 97% | 37.1 | 85% |
| **SARS-CoV-2 nasal swab** | Positive | Positive | Positive | Positive | Positive |
| **Clinical** | **Sat. O₂** | 96% | 97% | 94% | 97% | 85% |
| **PaO₂/FiO₂** | **Clinical score** | Moderate | Moderate | Severe | Severe | Severe |
| **Emergency department presentation** | **SARS-CoV-2 nasal swab** | Positive | Positive | Positive | Positive | Positive |
| **Clinical** | **Sat. O₂** | 96% | 97% | 94% | 97% | 85% |
| **PaO₂/FiO₂** | **Clinical score** | Moderate | Moderate | Severe | Severe | Severe |

*Clinical score according to “Diagnosis and treatment protocol for novel coronavirus pneumonia” (https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis. and.Treatment.of.COVID-19.V7.pdf).
From "Ente Ospedaliero Ospedale Galliera and IRCCS G. Gaslini, Genova, Italy. E-mail: marcogattorno@gaslini.org.

*These authors contributed equally to this work.

Disclosure of potential conflict of interest: R. Caorsi receives speaker’s fees and has consultancies for Novartis and SOBI. A. Ravelli receives speaker’s fees and has consultancies for Novartis and SOBI. M. Gattorno receives speaker’s fees and has consultancies for Novartis and SOBI. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.

2. Zhang Y, Gao Y, Qiao L, Wang W, Chen D. Inflammatory response cells during acute respiratory distress syndrome in patients with coronavirus disease 2019 (COVID-19) [published online ahead of print April 13, 2020]. Ann Intern Med. https://doi.org/10.7326/L20-0227.

3. Metha P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunesuppression. Lancet 2020;395:1033-4.

4. Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19 [published online ahead of print April 15, 2020]. Arthritis Rheumatol. https://doi.org/10.1002/art.41285.

5. Sanders JM, Monogue ML, Jodkowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review [published online ahead of print April 13, 2020]. JAMA. https://doi.org/10.1001/jama.2020.6019.

6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention [published online ahead of print February 24, 2020]. JAMA. https://doi.org/10.1001/jama.2020.2648.

7. Shakoor B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Crit Care Med 2016;44:275-8.

8. Elrose EM, Weiser P, Crayne CB, Haines H, Mannion ML, Stoll ML, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. Arthritis Rheumatol 2020;72:326-34.

Available online May 11, 2020. https://doi.org/10.1016/j.jaci.2020.05.002

Complement activation in patients with COVID-19: A novel therapeutic target

To the Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the coronavirus responsible for the current pandemic of coronavirus disease 2019 (COVID-19), whose very broad clinical spectrum ranges from minor signs and symptoms such as cough and mild fever to severe pneumonia with dyspnea, tachypnea, and impaired gas exchange, leading to severe and life-threatening manifestations in approximately 15% of infected patients. Increased levels of proinflammatory cytokines and coagulation...