Sarilumab (IL-6R antagonist) in critically ill patients with cytokine release syndrome by SARS-CoV2

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Abstract
Blocking IL-6 pathways with sarilumab, a fully human anti–IL-6R antagonist may potentially curb the inflammatory storm of SARS-CoV2. In the present emergency scenario, we used “off-label” sarilumab in 5 elderly patients in life-threatening condition not candidates to further active measures. We suggest that sarilumab can modulate severe COVID-19-associated Cytokine Release Syndrome.

Abbreviations: CRP = C-reactive protein, CRS = cytokine release syndrome, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: covid-19, critically ill, sarilumab, SARS-CoV-2 infection

1. Introduction
Facing the second wave of this COVID-19 outbreak, the spread of positive cases worldwide has brought a landscape of fear and respect with a maddening increase of cases over 122,036,229 and 2,694,915 deaths at March 15th.[1–3] However, several trials are ongoing to consider biological therapy as an alternative for unresponsive and life-threatening cases of cytokine release syndrome (CRS).[4–7]

2. Objective
We recently hypothesized that blocking IL-6 pathways with sarilumab(Kevzara), a fully human anti–IL-6R antagonist monoclonal antibody that binds membrane bound and soluble human IL-6R with high affinity, may potentially curb the inflammatory storm.[8,9] In the present emergency, according to our hospital guidelines we used “off-label” sarilumab in cases of critically advanced CRS, considering the higher 10-fold increase affinity for the receptor that sarilumab presents over tocilizumab.[10,11]

3. Methods
In this retrospective, single-centre observational report, we describe a case-series of 5 patients with severe, progressive and life-threatening severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) infection. All patients or their legal representatives gave oral informed consent. An expert committee prescribed the therapy according to more than one of the following criteria:
1. Age-adjusted Charlson Comorbidity Index scores <4,[12]
2. Interstitial pneumonia with severe respiratory failure (score ≥ 2),
3. rapid respiratory worsening requiring noninvasive or invasive ventilation (score ≥ 3 on the COVID respiratory severity scale),

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How to cite this article: Corominas H, Castellvi I, Diaz-Torné C, Matas L, de la Rosa D, Mangues MA, Moya P, Poma V, Benito N, Moga E, Sosa Nd, Casademont J, Domingo P, Sarilumab (IL-6R antagonist) in critically ill patients with cytokine release syndrome by SARS-CoV2. Medicine 2021;100:19(e25923). Received: 17 December 2020 / Received in final form: 8 April 2021 / Accepted: 12 April 2021
http://dx.doi.org/10.1097/MD.00000000000025923
the presence of severe systemic inflammatory response criteria was fully present: high levels of D-dimer (>1500 ng/mL) or progressively increasing D-dimer or alternatively high levels of IL-6 (>40 pg/mL).

General exclusion criteria for IL-6R antagonist therapy were: AST/ALT values greater than 5 times the upper limit of normality, neutrophils <500 cells/μL, platelets <50,000 cells/mm, documented sepsis by pathogens other than SARS-CoV-2, presence of comorbidity that can lead, according to clinical judgment, to a poor prognosis, complicated diverticulitis or intestinal perforation, or ongoing skin infection (uncontrolled pyodermitis with antibiotic treatment). The use of IL-6R was approved in strict compliance with the Hospital Ethics Committee with the given code (IRS-TOC-2020-01).

4. Results

Our 5 SARS-CoV-2 elderly patients, 3 men and 2 women, (median age: 72–74, [range: 62–79]), with good quality of life age adjusted Charlson <4) previous to the outbreak, when first admitted to hospital received hydroxychloroquine plus azithromycin. When they presented radiological progression, increased oxygen needs, and/or worsening of biological parameters, they were considered candidates to sarilumab.

Four of them were on noninvasive ventilation (NIV), and 1 was on invasive mechanical ventilation. An average median peak of the blood markers present before receiving sarilumab: CRP: 247.6 (mg/dL) (range: 123–480), LDH: 467 (U/L) (range: 309–766), creatine phosphokinase: 135 (U/L) (range: 44–179), Ferritin: 967.7 (μg/L) (range: 319–2529), IL-6: 167.2 (pg/mL) (range: 65.2–380), with an average decrease in lymphocyte count: 0.96 (x10⁹/L) (0.47–1.7) significantly improved after a single dose of sarilumab 200 mg sc. Clinical and serological variables of improvement are seen in Table 1. Two patients died; one with previous chronic obstructive pulmonary disease and obesity, and the other with high chronic kidney disease grade. Among both we observed the highest CRP: 480 (mg/dL), ferritin level: 3394 (μg/L), D-Dimer: 83275 (ng/mL), IL-6: 380 (pg/mL) and the lowest lymphocyte count: 0.45 (x10⁹/L). In the follow-up 3 patients fully recovered and were discharged home with improvement in the control chest X-Ray.

5. Discussion

Sarilumab, is a fully human anti–IL-6R antagonist monoclonal antibody that binds membrane bound and soluble human IL-6R with high affinity to treat adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to 1 or more disease-modifying antirheumatic drugs. Sarilumab, inhibits IL-6-mediated signaling pathway which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3, only in the presence of IL-6. IL-6 also stimulates diverse cellular responses such as proliferation, differentiation, survival, and apoptosis and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP) and serum amyloid. Scarcely existing evidence supports its use in the case of CRS, and has only been described in 4 previous reports in COVID-19.[13–17] Those 5 patients were in life-threatening critical condition not candidates to further active measures, neither to tocilizumab therapy because of comorbidities, limited access or temporary lack

| Table 1 | Other treatments | ETO/NIV | CRP (mg/dL) | LDH (U/L) | CPK (U/L) | Ferritin (μg/L) | Other treatments |
|---------|-----------------|---------|-------------|----------|-----------|----------------|-----------------|
| P1: W, 74y | HTN, DMI, AF | 60 | 68 | 211 | 600 | 180 | 14.3 | 152 | 287 | 310 |
| P2: M, 70y | HTN, DMI, AF | 100 | 70 | 221 | 350 | 180 | 0.1 | 0.1 | 0.1 |
| P3: M, 78y | HTN, DMI, AF | 150 | 120 | 221 | 350 | 180 | 0.1 | 0.1 | 0.1 |
| P4: W, 70y | HTN, DMI, AF | 200 | 140 | 221 | 350 | 180 | 0.1 | 0.1 | 0.1 |
| P5: W, 70y | HTN, DMI, AF | 250 | 160 | 221 | 350 | 180 | 0.1 | 0.1 | 0.1 |

**Note:** AF = atrial fibrillation, DMI = chronic obstructive pulmonary disease, CRP = C-reactive protein, DTI = diabetis mellitus, ETO = endotracheal intubation, HTN = hypertension, NIV = non invasive ventilation.
of stock. Therefore, sarilumab treatment was then started. Three out of 5 patients fully recovered and were later discharged home. We may argue the role that NIV and invasive ventilation played, but considering the worsening of those not treated with sarilumab, we assume the importance of the blockade of IL-6R. Interestingly, all blood active phase reactants improved after 24 hour. The crux of matter was the patients were treated late enough to avoid invasive ventilation measures. Thus, since they had an ominous clinical picture, advanced age and a late stage of the disease, our belief is that sarilumab therapy helped to reverse their CRS loop.

Currently, the optimal treatment for SARS CoV-2 pneumonia has not been defined yet. In a context of international emergency, we believed sarilumab therapy was a rationale option to minimize or reverse CRS in these critically ill patients. Ideally, we could have treated these patients sooner, but the emergency situation and the lack of recommendations for treating elderly patients prompted us to use sarilumab. Hopefully, in the near future we expect to have randomized controlled trials (23 studies registered in NCT, including ours) and data from observational studies (IBSP-COV-2020–28) to support clinical decisions.

In summary, we suggest that sarilumab can be useful in a global context of IL-6R antagonist indication, as an alternative to tocilizumab or other therapies targeted to modulate mild to severe COVID-19-associated CRS.

Author contributions

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