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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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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party. The datasets generated during and/or analyzed during the current study are publicly available.

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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/mm, platelets <50000 cells/mmc, 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: 72–2, [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: 0,93 (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.[10] 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.[9] Scarce 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
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	Comorbidities	Other treatments	ETI/NIV	CRP (mg/dl)			LDH (U/L)			CPK (U/L)			Ferritin (μg/L)			D-Dimer (ng/mL)			Outcome ($x10^9$/L)	IL-6 (pg/mL)			Limphocytes
				a	b	c	a	b	c	a	b	c	a	b	c	a	b	c		a	b	c	
P1: W, 76y	HTN, DMII, AF	lopinavir/ritonavir[a]	ETI	68	153	18	293	309	247	46	44	27	302	442	348	774			124,9	0,37	0,90	1,35	Discharged home 22 days after sarilumab
P2: W, 71y	HTN, DMII	hydroxychloroquine, plus azithromycin[b,**] hydroxychloroquine plus azithromycin[b]	NIV	221	330	15	608	528	292	424	159		3771	2529			2272	2036	–	0,97	0,89	1,76	Discharged home 19 days after sarilumab
P3: M, 78y	HTN, COPD, AF, Obesity	hydroxychloroquine plus azithromycin[b]	NIV	143	152	208	287	398	435	869	179	151	1198		3394		302	515	380	0,64	0,47	0,57	Death 2 days. after sarilumab
P4: W, 79y	HTN, DLP CKDIIIa,	hydroxychloroquine plus azithromycin[b] prednisolone 250 mg[c]	NIV	400	480			766	713		160			319			83275	31975	65,2		0,71	0,45	Death 6days after sarilumab
P5: M, 62y	HTN, DMII, hepatic fibrosis	hydroxychloroquine plus azithromycin[b]	NIV	76	123	25	331	334	221				326	581	461	727	856	1546	98,7	1,29	1,72	1,98	FiO_2:21%) 9 days after sarilumab

AF = atrial fibrillation, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DLP = dyslipidemia, DM = diabetes mellitus, ETI = endotracheal intubation, HTN = hypertension, NIV = non invasive ventilation.
[a]At admission.
[b]Before sarilumab.
[c]After sarilumab.
[**]Hydrochloroquine 400 mg/12h (1d) followed by 200 mg/12h (4 more days) plus azithromycin 500 mg/d (3 days).

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 (IIBSP-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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