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Severe Neutropenia after Sarilumab Administration in Two COVID-19 Patients: Case Reports and Literature Review

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Abstract

BACKGROUND: Two years have passed since the WHO declared a pandemic state for SARS-CoV2 infection. COVID-19 pathogenesis consists of a first viral phase responsible for early symptoms followed by an inflammatory phase, which is cytokine-mediated, responsible for late-onset signs up to acute respiratory distress syndrome. Considering that interleukin (IL)6 plays a key role in the development and maintenance of inflammation, drugs targeting both IL6 and IL6 receptors have been evaluated.

CASE REPORTS: The present study reports the cases of two hospitalized patients with severe respiratory COVID-19 treated with a single dose of intravenous sarilumab, a monoclonal anti-IL6 antibody, along with standard of care medications and high-flow oxygen therapy. Although a few days following sarilumab administration, clinical and biochemical conditions started ameliorating, these patients developed severe and self-limiting neutropenia.

CONCLUSION: Sarilumab may represent a promising weapon to treat the fearsome hyperinflammatory phase; however, more trials are needed to decide whether to use it in combination with other drugs or alone, and to better understand pharmacokinetics and side effects.

Introduction

Almost 2 years have passed since the WHO declared SARS-CoV2 outbreak a global pandemic [1]. Up to January 31, 2022, >380 million cases of SARS-CoV2 infections were reported and >5 million individuals succumbed to the disease worldwide. To date, a total of 11 million cases have been reported in Italy, 147,000 of which have not survived [2].

Uncontrolled systemic inflammation due to cytokines overexpression represents a critical element in the progression of COVID-19 to acute respiratory distress syndrome (ARDS) [3].

This nonspecific and harmful inflammatory response leads to alveolar damage because of inflammatory cells infiltration, pulmonary edema, and endothelial impairment along with microvascular thrombosis, playing a key role in the development of severe COVID-19 [3], [4], [5].

Interleukin (IL)-6 cascade has already been proposed as a potential target for immunomodulatory therapy to moderate systemic hyper-inflammation during SARS-CoV2 infection [6] [7].

Scientific literature and international guidelines [8] [9] suggest the use of tocilizumab, a recombinant monoclonal antibody, in addition to standard of care, due to its ability to lower the risk of respiratory deterioration, thus reducing mortality.

When tocilizumab is not available, sarilumab, a human monoclonal antibody targeting IL-6 soluble receptors which is already approved for rheumatoid arthritis treatment, appears for a valid alternative for IL-6 blockade [10].

Neutrophil cells express soluble IL-6 receptor (IL6-Rα) and IL-6 blockade may affect peripheral neutrophils concentration leading to neutropenia due to different suggested mechanisms [11].

Herein, we report the case of two patients with severe pulmonary forms of COVID-19, requiring

high-flow nasal oxygenation, who developed severe self-limiting neutropenia after sarilumab administration.

Case Presentation

First patient

Upon admission, the patient was feverish (T 39.5°C), blood pressure (BP) was 150/75 mmHg, heart rate (HR) was 100 bpm, oxygen saturation rate was 95% in Venturi mask (VM) 8L/min FiO_2 35%.

Blood tests revealed elevated inflammatory markers levels along with neutrophilic leukocytosis (Table 1). Chest computed tomography (CT) of scan revealed bilateral interstitial pneumonia (Figure 1).

Enoxaparin, dexamethasone, and piperacillin/tazobactam were administered.

On the 3rd day, arterial blood analysis showed that PO_2 49 mmHg, PCO_2 28.5 mmHg, pH 7.45, and PaO_2/FiO_2 were 139. High-flow nasal cannula (HFNC) (Optiflow™ Nasal High Flow Therapy delivered by AIRVO™ 2) 60 l/min, FiO_2 60% was arranged. The next day, sarilumab 400 mg i.v., single dose, was administered.

Within 48 h, arterial blood analysis revealed progressive amelioration (PaO_2/FiO_2 was 122). Although serum inflammatory marker levels started diminishing (C-reactive protein [CRP] levels 0.29 mg/dl), blood tests showed leukopenia with neutropenia, reaching a nadir 9 days after sarilumab infusion (2,000/mmc, 12.1% neutrophils). Neutropenia resolved within 7 days without treatment.

HFNC ventilation was stopped within 11 days. Subsequently, a VM was used for another 5 days, gradually reduced over this period of time.

Second patient

Upon admission, the patient was feverish (T 39.5°C), BP was 145/55 mmHg, HR was 100 bpm, oxygen saturation was 97% in VM 6 L/min FiO_2 31%.

Blood tests revealed high inflammatory marker levels along with high D-dimer levels and hypertransaminasemia (Table 1). Chest CT scan showed bilateral interstitial pneumonia (Figure 2). The patient started enoxaparin, dexamethasone, and piperacillin/tazobactam treatment.

Since arterial blood analysis revealed PaO_2 57 mmHg, PCO_2 31 mmHg, pH 7.5, and PaO_2/FiO_2 ratio was 93, along with deterioration of chest imaging, HFNC ventilation (60L/min FiO_2 60%) was started. Sarilumab 400 mg i.v. was administered within 24 h after HFNC initiation.

Within 48 h, her respiratory performances and blood arterial analysis began to improve (PaO_2/FiO_2 ratio was 136). Inflammatory marker levels started decreasing. However, 7 days after sarilumab administration, the patient's laboratory tests showed leukopenia with neutropenia (2,700/mmc, 18.9% neutrophils). Neutropenia resolved within 7 days without treatment.

HFNC treatment was gradually reduced and switched to VM first and nasal cannula then, until hospital discharge.

Table 1: Clinical and epidemiological patient's characteristics

Characteristics	Patient 1	Patient 2
Age (years)	84	73
Sex	Female	Female
SARS-CoV-2 vaccination	No	No
Comorbidities	Hypertension	Hypertension, GERD, major depressive disorder
Home therapy	None	Candesartan, alprazolam, pantoprazole
Days between admission and HFNC treatment initiation	3	2
Chest CT findings	Bilateral interstitial pneumonia along with vast consolidations	Bilateral interstitial pneumonia and consolidations within bronchiectasis
Days between the onset of symptoms and hospital admission	12	7
WBC, cells/mmc (4000-10,000)	12,900	8400
Neutrophils, % (40-75)	86	83.8
Lymphocytes, % (25-50)	9.9	10.6
Monocytes, % (2-10)	3.9	5.5
Platelets, cells/mmc × 10^3 (150-400)	321	172
Haemoglobin, g/dl (12-16)	13.6	13.9
AST, UI/l (15-35)	40	73
ALT, UI/l (15-35)	27	107
LDH, UI/l (80-250)	430	526
Creatinine, mg/dl (0.8-1.2)	0.6	0.57
CRP, mg/dl (0-0.5)	10.04	12.99
ESR, mm/h (0-10)	56	66
D-dimer, ng/ml (<250)	680	18,847
Ferritin, ng/ml (20–200)	796	1118
Lowest PaO2/FiO2 ratio	94	93
Antibiotic therapy (duration)	Piperacillin/tazobactam (10 days) Levofloxacin (7 days)	Piperacillin/tazobactam (11 days)
Others therapies (duration)	Enoxaparin 6000 UI s.c. (28 days), dexamethasone 6 mg i.v. (26 days)	Enoxaparin 6000 UI s.c. (18 days), dexamethasone 6 mg i.v. (16 days)
Days on HFNC	11	9
Sarilumab dose (number of doses)	400 mg i.v. (single dose)	400 mg i.v. (single dose)
Days from admission to sarilumab	4	3
Time to hospital discharge (days)	28	18

GERD: Gastroesophageal reflux disease, WBC: White blood cell count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HFNC: High-flow nasal cannula, SARS-CoV2: Severe acute respiratory syndrome coronavirus 2, CT: Computed tomography.

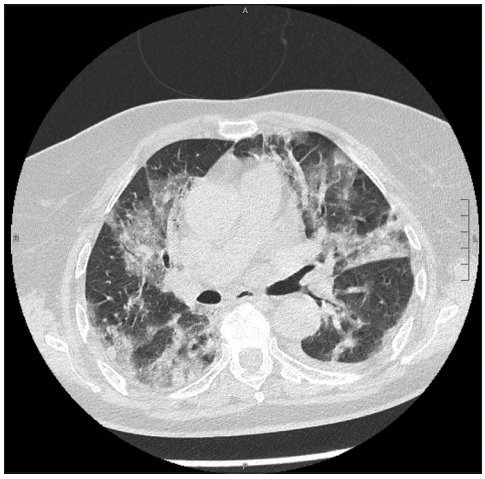

Figure 1: First patient thorax computed tomography scan

Discussion

Up to now, SARS-CoV2 infection pathophysiology remains mostly unclear; both immune and inflammatory responses seem to play a key role in disease development and duration, especially as regards its severe form [3].

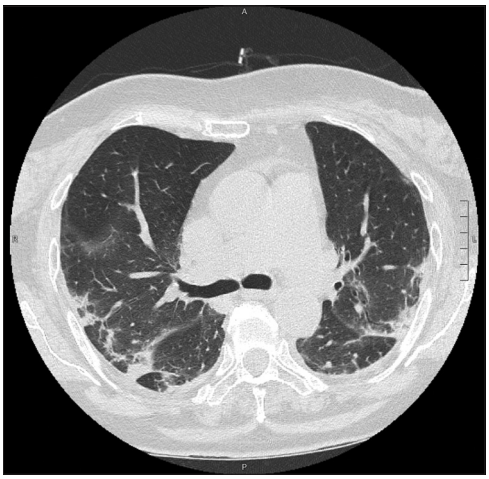

Figure 2: Second patient thorax computed tomography scan

Although we could intervene during the first phase of infection (viral phase) with some antiviral drugs or monoclonal antibodies, to avoid disease progression, it is the second phase (inflammatory phase) that puts clinicians to the test because of its severity, complexity, and lack of standardized treatments [3] [4].

Several studies report that COVID-19 causes the so-called Cytokine Release Syndrome (CRS), leading to dysregulated immune response up to ARDS [3] [4] [12] [13].

Multiple proinflammatory cytokines have been investigated as the cause of CRS and, among them, IL-6 resulted in one of the most studied due to its fundamental role in inflammatory pathways.

IL-6 has been identified as both an inflammatory/prognostic marker since its levels correlate with inflammation state and a therapeutic target [6] [7].

Monoclonal antibodies targeting IL-6 and IL6-Rα are recommended by Italian and American guidelines to treat patients with severe and critical COVID-19 [8] [9].

Sarilumab, a humanized monoclonal antibody (IgG1 subtype), specifically binds both soluble and membrane-attached IL6-Rα; it inhibits IL6-mediated pathways involving glycoprotein 130 along with STAT-3, signaling transducer and transcription activator [7].

Sarilumab has been investigated in a small number of studies whose results are not conclusive [14] [15] [16].

To date, only few randomized controlled trials have been published about sarilumab administration in COVID-19 patients and no specific meta-analyses have been performed yet.

In the study performed by REMAP-CAP collaborative group [17], 48 patients were assigned to one dose of 400 mg sarilumab i.v. administration; results showed that sarilumab improved in-hospital survival compared with usual care.

A larger study, performed by Lescure *et al*. [17] on 420 subjects, did not demonstrate efficacy of sarilumab as regards outcome and survival rates in patients hospitalized with severe COVID-19 and receiving supplemental oxygen, despite improved recovery time.

CORIMUNO-19 group performed an open-label, randomized, controlled trial with 148 patients randomly assigned to sarilumab or SOC, with half patients in the sarilumab group that was treated with a second dose [18]. This trial did not highlight any effect of sarilumab in patients with moderate to severe COVID-19 in terms of mortality rate nor for the decreasing proportion of patients needing noninvasive ventilation.

The cases we reported developed severe pulmonary disease due to SARS-CoV2 between 10 and 15 days from infection probably because of excessive proinflammatory response.

All our patients have multiple risk factors for serious COVID-19 – age >70 y.o., multiple comorbidities, polypharmacy. CT findings showed the presence of bilateral interstitial lung involvement and arterial blood examination displayed gradual respiratory parameters deterioration.

Each patient received oxygen administration through high flow nasal cannula, achieving a better peripheral saturation along with blood gas analysis amelioration [19] [20].

Furthermore, a single dose of intravenous sarilumab was administered.

Before sarilumab administration, patients were screened for latent or active infections

such as hepatitis C virus, HIV, and hepatitis B virus [20] [21] [22] [23] [24] [25] [26].

Within 48–72 h after anti-IL6-treatment, patients' respiratory conditions started improving, along with improved blood gas examination and clinical parameters.

We used CRP with a cut-off of 75 mg/L as a surrogate marker of systemic inflammation to guide sarilumab administration and to assess patients' conditions.

Antibiotic therapy was chosen based on local bacterial epidemiology, patients' previous antibiotic treatments, and thorax CT scan results [27] [28] [29].

Furthermore, standard of care therapy (enoxaparin and dexamethasone) was administered since admission, following Italian guidelines.

As regard scientific literature on sarilumab adverse drug reactions, although with some limitations (absence of a control group, single center setting, concomitant treatments), Gremese *et al*. [15] did not register neither serious adverse events nor secondary infections related to the treatment with sarilumab. In the study of Lescure *et al*. [10], the occurrence of adverse events of different severity was similar between both the treatment and the placebo group [30].

No serious adverse events have been reported in the REMAP-CAP study [17], and CORIMUNO-19 group [18] reported few cases of temporary neutropenia that is a common side effect of all IL-6 blockers. In the same study, a non-statistically significant increased number of bacterial infections was reported in the sarilumab group (12 patients) compared to the control group (seven patients).

Although transient neutropenia has been observed in several studies involving patients affected by autoimmune diseases such as rheumatoid arthritis treated with drugs targeting IL-6 cascade, serious infection rate in these patients did not appear to be increased, suggesting that blocking IL-6 pathways may influence neutrophils number without compromising their function [31], [32].

Wright *et al*., observing *in vitro* the effect of anti-IL-6 drugs on neutrophil population, showed that anti-IL-6 induced neutropenia is not directly determined by augmented neutrophil apoptosis [11].

There are no definitive data about neutrophil count reduction after IL-6 blockade, but only several hypotheses supported by scientific literature [11].

Decreased neutrophil count may be the result of a different cells distribution between circulating and marginating pool, due to IL6-blocking drug effects on L-selectin and P- selectin ligand expression on neutrophils surface. Because of the role of IL-6 in accelerating neutrophils release from the bone marrow to circulation, anti-IL-6 drugs may provoke an increase in transit time, causing transient neutropenia [11] [33].

Significantly, literature data reveal that while total neutrophil count may decline after anti-IL-6 drugs, the remaining neutrophils are totally functional without impairment in their ability to mount a respiratory burst or phagocytose bacteria [33] Moreover, transient nature of the neutropenia suggests that neutrophil counts begin to resolver within days, minimizing the risk of serious infection [33].

Larger randomized controlled trials, both *in vivo* and *in vitro*, together with meta-analyses are needed to detect the real effect of sarilumab administration in COVID-19 patients as regard clinical efficacy and immune effects.

Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Patient consent for publication

Written informed consent was obtained from the patients for the publication of these case reports.

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