# Sarilumab administration in patients with severe COVID-19: A report of four cases and a literature review

ANDREA MARINO[1,2], EDOARDO CAMPANELLA[3], MANUELA CECCARELLI[2], LICIA LAROCCA[2], CARMELO BONOMO[1], CRISTINA MICALI[3], ANTONIO MUNAFÒ[4], BENEDETTO MAURIZIO CELESIA[2], GIUSEPPE NUNNARI[3] and BRUNO CACOPARDO[2]

[1]Department of Biomedical and Biotechnological Sciences, University of Catania, I-95124 Catania; [2]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, ARNAS Garibaldi Hospital, University of Catania, I-95122 Catania; [3]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, I-98122 Messina; [4]Unit of Clinical Toxicology, Policlinico G. Rodolico, School of Medicine, University of Catania, I-95123 Catania, Italy

Received February 27, 2022; Accepted April 18, 2022

DOI: 10.3892/wasj.2022.159

**Abstract.** Almost 2 years have passed since the World Health Organization declared a pandemic state for severe acute respiratory syndrome coronavirus 2 infection. The pathogenesis of coronavirus disease 2019 (COVID-19) consists of an initial viral phase responsible for early symptoms followed by an inflammatory phase, which is cytokine-mediated, responsible for late-onset symptoms, culminating in acute respiratory distress syndrome. Considering that IL-6 plays a key-role in the development and maintenance of inflammation, drugs targeting both IL-6 and IL-6 receptors have been evaluated. The present study reports the cases of four hospitalized patients with severe respiratory COVID-19 treated with a single dose of sarilumab, a monoclonal anti-IL-6 antibody, along with standard of care medications and oxygen therapy. A few days following sarilumab administration, the clinical and biochemical conditions began to improve, until the discontinuation of $O_2$ therapy and discharge. The present study demonstrates that sarilumab may represent a promising drug that may be used to treat the hyperinflammatory phase; however, further trials are required to determine whether it should be used combination with other drugs or alone, and to better understand the pharmacokinetics and related side-effects.

*Correspondence to:* Dr Manuela Ceccarelli, Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, ARNAS Garibaldi Hospital, University of Catania, Via Palermo 636, I-95122 Catania, Italy
E-mail: manuela.ceccarelli86@gmail.com

*Key words:* COVID-19, sarilumab, severe acute respiratory syndrome coronavirus 2 infection, anti-IL-6 drugs, cytokine storm

## Introduction

Almost two years have passed since the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a global pandemic (1). The infection rate became markedly stable and some authors, considering the interactions between coronavirus disease 2019 (COVID-19) and other non-communicable diseases, refer to this situation as a 'syndemic' (2,3).

Up to January 31, 2022, >380 million cases of SARS-CoV-2 infection were reported and over five 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 (4). It is now clear that an uncontrolled systemic inflammation represents a critical element in the progression of COVID-19 to acute respiratory distress syndrome (ARDS) (5). This non-specific and deleterious inflammatory response appears to lead to alveolar damage due to inflammatory cell infiltration, pulmonary edema and endothelial impairment along with microvascular thrombosis, playing a key role in the development of severe COVID-19 (6,7).

Of note, dexamethasone treatment has been shown to be associated with improved outcomes in patients with severe COVID-19 (8). The IL-6 cascade has already been proposed as a potential target for immunomodulatory therapy to moderate systemic hyper-inflammation during SARS-CoV-2 infection (9,10).

Scientific literature and international guidelines (11,12) suggest the use of tocilizumab, a recombinant monoclonal antibody, in addition to standard of care treatment, due to its ability to lower the risk of respiratory deterioration, thus reducing the mortality rate. In the case that tocilizumab is not available, sarilumab, a human monoclonal antibody targeting IL-6 soluble receptors, which is already approved for the treatment of rheumatoid arthritis, represents a valid alternative for IL-6 blockade (13). Considering that IL-6 has multiple pathways with varying effects, both positive and negative on inflammation and homeostatic control, it is arduous for

clinicians to determine the correct therapeutic window for the administration of anti-IL-6 drugs (13).

The present study describes cases of 4 patients with severe pulmonary forms of COVID-19, requiring high-flow nasal oxygenation along with dexamethasone administration, who were successfully discharged following sarilumab administration.

## Case report

*Case 1*. Upon admission to the ARNAS Garibaldi Hospital, Catania, Italy, the patient was feverish (temperature, 38.5˚C), blood pressure (BP) was 125/60 mmHg, heart rate (HR) was 62 bpm, and oxygen saturation was 91% in room air. He was administered $O_2$ therapy with a Venturi mask (VM) at 12 l/min (fraction of inspired oxygen ($FiO_2$, 60%). Blood tests revealed elevated inflammatory marker levels (Table I) and a thoracic CT scan revealed bilateral interstitial pneumonia (Fig. 1). Treatment with prophylactic enoxaparin, dexamethasone and piperacillin/tazobactam was commenced.

On the 4th day, due to the worsening of oxygen saturation, an arterial blood analysis was performed, revealing partial pressure of oxygen ($PaO_2$) levels of 62.3 mmHg, partial pressure of carbon dioxide ($PCO_2$) levels of 30.2 mmHg, pH 7.39 and a $PaO_2/FiO_2$ ratio of 103.

Oxygen ventilation with a high flow nasal cannula (HFNC; Optiflow™ Nasal High Flow Therapy delivered by AIRVO™ 2; Fisher & Paykel Healthcare), 60 l/min, $FiO_2$ 60% was administered, and on the same day, the patient was administered a single dose of sarilumab at 400 mg intravenously. Furthermore, levofloxacin 500 mg/day was empirically added to extend the antibiotic coverage.

Within 24 h from sarilumab administration, his clinical condition ameliorated, and arterial blood analysis improved ($PaO_2/FiO_2$ ratio of 140). The levels of serum inflammatory markers decreased [C-reactive protein (CRP) levels, 0.44 mg/dl]. HFNC ventilation was continued for a further 7 days (8 days overall), and the patient was gradually weaned off of $O_2$ therapy following a further 5 days.

*Case 2*. Upon admission (to the same hospital as mentioned above), the patient was afebrile, BP was 135/60 mmHg, HR was 110 bpm, and oxygen saturation was 96% with a nasal cannula (NC) 3l/min. Blood tests revealed high inflammatory marker levels (Table I). A thoracic CT scan revealed bilateral interstitial pneumonia (Fig. 2). Treatment with dexamethasone and piperacillin/tazobactam was commenced.

Despite pharmacologic treatment and $O_2$ supplementation, his respiratory functions continued to deteriorate. Blood gas analysis with the VM at 12 l/min, $Fi0_2$ 60%, revealed $PaO_2$ at 59 mmHg, $PCO_2$ at 39 mmHg, pH 7.47 and a $PaO_2/FiO_2$ ratio of 98. HFNC ventilation (60 l/min, $FiO_2$ 60%) was commenced on the 4th day from admission, and sarilumab at 400 mg intravenously was administered within 24 h.

Within 48 h from the sarilumab administration, his clinical condition, laboratory tests (CRP levels 1.32 mg/dl), and blood gas analysis ($PaO_2/FiO2$, 121) improved. HFNC treatment was steadily reduced; this was switched to a VM at 9 days following HFNC initiation, and the patient was also gradually weaned off this as well.

*Case 3*. Upon admission (to the same hospital as mentioned above), the patient was feverish (temperature, 39.5˚C), BP was 150/75 mmHg, HR was 100 bpm, the oxygen saturation rate was 95% with a VM at 8 l/min and a $FiO_2$ of 35%. Blood tests revealed elevated inflammatory marker levels along with neutrophilic leukocytosis (Table I). A chest CT scan revealed bilateral interstitial pneumonia (Fig. 3). Enoxaparin 6,000 U/day, dexamethasone 6 mg/day and piperacillin/tazobactam 4.5 g/three times/day were administered.

On the 3rd day, arterial blood analysis revealed a $PaO_2$ of 49 mmHg, $PCO_2$ of 28.5 mmHg, pH 7.45 and a $PaO_2/FiO_2$ ratio of 139. HFNC was commenced at 60 l/min, and a $FiO_2$ of 60% was arranged. The following day, sarilumab was administered intravenously at a single dose of 400 mg.

Within 48 h, arterial blood analysis revealed progressive amelioration in the patient's condition ($PaO_2/FiO_2$ was 122). Although serum inflammatory marker levels began to decrease (CRP levels, 0.29 mg/dl), blood tests revealed leukopenia with neutropenia, reaching a nadir 9 days following sarilumab infusion (2,000/mmc, 12.1% neutrophils). Neutropenia resolved within 7 days without treatment. HFNC ventilation was terminated within 11 days. Subsequently, a VM was used for a further 5 days, and this was gradually reduced over this period of time.

*Case 4*. Upon admission (to the same hospital as mentioned above), the patient was feverish (temperature, 39.5˚C), BP was 145/55 mmHg, HR was 100 bpm, oxygen saturation was 97% with a VM at 6 l/min and a $FiO_2$ of 31%. Blood tests revealed high inflammatory marker levels along with high D-dimer levels and hypertransaminasemia (Table I). A chest CT scan revealed bilateral interstitial pneumonia (Fig. 4). The patient was commenced on treatment with enoxaparin 6,000 U/day, dexamethasone 6 mg/day and piperacillin/tazobactam 4.5 g/three times/day.

Since arterial blood analysis revealed $PaO_2$ of 57 mmHg, $PCO_2$ of 31 mmHg, pH 7.5, and a $PaO_2/FiO_2$ ratio of 93, along with the deterioration of chest imaging, HFNC (60 l/min; $FiO_2$ 60%) was commenced. Sarilumab was administered intravenously at 400 mg within 24 h after the initiation of HFNC.

Within 48 h, the patient's respiratory performances and blood arterial analysis began to improve ($PaO_2/FiO_2$ ratio was 136). Inflammatory marker levels also began to decrease. However, 7 days following the administration of sarilumab the patient's laboratory tests revealed 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 then NC, until hospital discharge.

## Discussion

To date, SARS-CoV-2 infection pathophysiology remains mostly unclear, arguably as it is not attributable only to the virus; in fact, both immune and inflammatory responses appear to play a key role in disease development and duration, particularly as regards its severe form.

In order to avoid disease progression, intervention can take place during the first phase of infection (viral phase) with certain antiviral drugs (remdesivir, molnupiravir,

Table I. Demographics, clinical characteristics at the time of admission, treatment and outcomes of the 4 patients with COVID-19.

| Characteristics | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Age, years | 75 | 73 | 84 | 73 |
| Sex | Male | Male | Female | Female |
| SARS-CoV-2 vaccine (no. of doses) | No | Yes (2 doses of BNT162b2) | No | No |
| Comorbidities | Hypertension, coronary disease with previous percutaneous revascularization. | Atrial fibrillation, diabetes mellitus, COPD | Hypertension | Hypertension, GERD, major depressive disorder |
| Home therapy | Clopidogrel, bisoprolol, ramipril, amlodipine, cardioaspirin, omeprazole | Methimazole, insulin, pantoprazole, amlodipine, propranolol, apixaban | None | Candesartan, alprazolam, pantoprazole |
| Days between admission and HFNC treatment initiation | 4 | 4 | 3 | 2 |
| Chest CT findings | Bilateral honeycombing pattern, fibrotic reticulation, and consolidations | Bilateral interstitial pneumonia along with consolidations and bilateral pleural effusion | Bilateral interstitial pneumonia along with vast consolidations | Bilateral interstitial pneumonia, and consolidations within bronchiectasis |
| Days between the onset of symptoms and hospital admission | 15 | 7 | 12 | 7 |
| Laboratory finding; unit (reference range) | | | | |
| WBC, cells/mmc (4,000-10,000) | 7,100 | 6,000 | 12,900 | 8,400 |
| Neutrophils, % (40-75) | 80.5 | 63.8 | 86 | 83.8 |
| Lymphocytes, % (25-50) | 10.7 | 26.2 | 9.9 | 10.6 |
| Monocytes, % (2-10) | 8.6 | 8.8 | 3.9 | 5.5 |
| Platelets, cells/mmc x103 (150-400) | 230 | 85 | 321 | 172 |
| Hzemoglobin, g/dl (12-16) | 13.3 | 13 | 13.6 | 13.9 |
| AST, UI/l (15-35) | 29 | 45 | 40 | 73 |
| ALT, UI/l (15-35) | 24 | 16 | 27 | 107 |
| LDH, UI/l (80-250) | 362 | 411 | 430 | 526 |
| Creatinine, mg/dl (0.8-1.2) | 1.28 | 0.84 | 0.6 | 0.57 |
| CRP, mg/dl (0-0.5) | 9.95 | 12.34 | 10.04 | 12.99 |
| ESR, mm/h (0-10) | 54 | 29 | 56 | 66 |
| D-dimer, ng/ml (<250) | 2,013 | 883 | 680 | 18,847 |
| Ferritin, ng/ml (20-200) | 814 | 522 | 796 | 1,118 |
| Lowest $PaO_2/FiO_2$ ratio | 103 | 98 | 94 | 93 |
| Antibiotic therapy (duration) | Piperacillin/tazobactam (12 days), levofloxacin (7 days) | Piperacillin/tazobactam (12 days) | Piperacillin/tazobactam (10 days) levofloxacin (7 days) | Piperacillin/tazobactam (11 days) |

Table I. Continued.

| Characteristics | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Others therapies (duration) | Enoxaparin 6,000 UI s.c. (18 days), dexamethasone 6 mg i.v. (18 days) | Dexamethasone 6 mg i.v. (22 days) | Enoxaparin 6,000 UI s.c. (28 days), dexamethasone 6 mg i.v. (26 days) | Enoxaparin 6,000 UI s.c. (18 days), dexamethasone 6 mg i.v. (16 days) |
| Days on HFNC | 8 | 9 | 11 | 9 |
| Sarilumab dose (number of doses) | 400 mg i.v. (single dose) | 400 mg i.v. (single dose) | 400 mg i.v. (single dose) | 400 mg i.v. (single dose) |
| Days from admission to sarilumab | 5 | 5 | 4 | 3 |
| Time to hospital discharge (days) | 18 | 24 | 28 | 18 |

COPD, chronic obstructive pulmonary disease; 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; i.v., intravenous; s.c., subcutaneous.



Figure 1. Thoracic CT scan of case 1. A, anterior; P, posterior; R, right; L, left.



Figure 2. Thoracic CT scan of case 2. A, anterior; P, posterior; R, right; L, left.



Figure 3. Thoracic CT scan of case 3. A, anterior; P, posterior; R, right; L, left.

nirmatrelvir/ritonavir) or monoclonal antibodies (sotrovimab), administering these within the correct time lapse. However, the second phase (inflammatory phase) is more severe, and thus it is difficult to treat due to its severity, complexity and lack of standardized treatments (14).

It has been reported that COVID-19 causes cytokine release syndrome (CRS), leading to a dysregulated immune

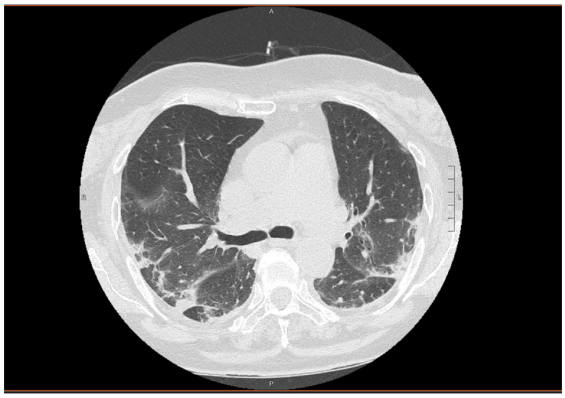

Figure 4. Thoracic CT scan of case 4. A, anterior; P, posterior; R, right; L, left.

response, culminating in ARDS, which is also determined by the up- and downregulation of the expression of several genes directly stimulated by SARS-CoV-2 infection (15).

CRS is considered an immune system overreaction response developing in an unregulated manner, the same pathogenetic mechanism which underlines autoimmune and hematological diseases (16,17). As confirmation, drugs to treat this phase are also administered against autoimmune disorders (16).

Various proinflammatory cytokines have been investigated as the cause of CRS and, among these, IL-6 is one of the most extensively studied due to its crucial role in inflammatory pathways. IL-6 has been studied as both an inflammatory/prognostic marker, since its levels are associated with the inflammatory state and a therapeutic target (13). Monoclonal antibodies targeting IL-6 and IL-6 receptors are recommended by Italian and American guidelines for the treatment of patients with severe and critical COVID-19 (14).

Sarilumab, a humanized monoclonal antibody (IgG1 subtype), specifically binds both soluble and membrane-attached IL-6 receptors (IL6-Rα); it inhibits IL6-mediated pathways involving glycoprotein 130 (gp130) along with STAT-3. Sarilumab has been investigated in a few studies, the results of which are not conclusive (13). Della-Torre *et al* (18) reported data from 28 patients with COVID-19 treated with a single dose of sarilumab intravenously, and demonstrated a decrease in recovery time; however, no statistically significant differences in terms of mortality and overall improvement between patients treated with standard of care were reported.

Gremese *et al* (19) studied 53 patients treated with sarilumab, almost all of which received a second infusion; 14 of these patients were from the intensive care unit (ICU) and exhibited an improvement in clinical conditions along with a reduction in oxygen supplementation therapy; in addition, more than half of the ICU patients exhibited clinical amelioration following sarilumab administration. Although on a smaller sample size, similar results were demonstrated in the study by Benucci *et al* (20) on 8 patients treated with sarilumab.

To date, only a few randomized controlled trials (13) have been published on sarilumab administration in patients with COVID-19 and no specific meta-analyses have been performed to date, at least to the best of our knowledge. In the study performed by the REMAP-CAP collaborative group (21), 48 patients were assigned to one dose of 400 mg sarilumab intravenous administration; the results revealed that sarilumab improved in-hospital survival compared with usual care.

A larger study, performed by Lescure *et al* (12) on 420 subjects, did not demonstrate the efficacy of sarilumab as regards the outcomes and survival rates of patients hospitalized with severe COVID-19 and receiving supplemental oxygen, despite an improved recovery time.

The CORIMUNO19 group performed an open-label, randomized, controlled trial with 148 patients randomly assigned to sarilumab or standard of care, with half of the patients in the sarilumab group treated with a second dose (22). That trial did not highlight any effect of sarilumab in patients with moderate to severe COVID-19 in terms of mortality rate nor on the decreasing proportion of patients requiring non-invasive ventilation.

The cases reported in the present study developed severe pulmonary disease due to SARS-CoV2 between 10 and 15 days from infection, probably due to an excessive proinflammatory response. All the patients described herein had multiple risk factors for severe COVID-19 (an age >70 years, multiple comorbidities and polypharmacy). The results of CT scans revealed the presence of bilateral interstitial lung involvement and arterial blood examination displayed gradual respiratory parameters deterioration.

Among the patients in the present study, only one had received two doses of the anti-SARS-CoV-2 vaccine. Each patient received oxygen administration through HFNC, achieving a better peripheral saturation along with blood gas analysis amelioration (23,24). Furthermore, a single dose of sarilumab was intravenously administered to each patient, in accordance with Italian guidelines (AIFA) and IDSA guidelines (11,14).

Prior to the sarilumab administration, all the patients in the present study were screened for latent or active infections such as hepatitis C virus, human immunodeficiency virus and hepatitis B virus (25-31). Within 48-72 h following anti-IL-6 treatment, the patients' respiratory conditions began to improve, along with improved blood gas examination and clinical parameters. CRP levels at a cut-off value of 75 mg/l were used as a surrogate marker of systemic inflammation to guide the sarilumab administration and to assess the patients' conditions.

Antibiotic therapy was selected based on local bacterial epidemiology, the patients' previous antibiotic treatments and the thoracic CT scan results (31-34). Furthermore, standard of care therapy (enoxaparin and dexamethasone) was administered upon admission, following Italian guidelines.

Dexamethasone administration has been found to be highly variable across studies on sarilumab therapy, in contrast to trials on tocilizumab administration, in which the anti-IL-6 drug has been almost always administered together with corticosteroids. This difference may explain the diverse results between tocilizumab and sarilumab in favor of the former drug in previous studies; however, these data need to be clarified in larger-scale trials (35).

As regards the scientific literature on the adverse reactions associated with the use of sarilumab, although with some limitations (the absence of a control group, single-center

setting, concomitant treatments), Gremese *et al* (19) did not register severe adverse events or any secondary infections related to treatment with sarilumab. In the study by Lescure *et al* (12), the occurrence of adverse events of varying severity was similar between both the treatment and the placebo group.

No severe adverse events were reported in the REMAP-CAP study (21), and the CORIMUNO19 group (22) reported a few cases of temporary neutropenia that is a common side-effect of all IL-6 blockers. In the same study, a non-statistically significant increase in the number of bacterial infections was reported in the sarilumab group (12 patients) compared to the control group (7 patients).

In the present study, 2 of the patients described developed neutropenia following the sarilumab administration, which resolved within a few days without sequelae. Although it is limited, the authors' experience with sarilumab administration is in accordance with the findings in the literature as regards the percentage of recovery, time to oxygen weaning, safety of sarilumab and time to discharge (12-15).

In August 2020, the authors published the results of a small case series on tocilizumab administration in patients on HFNC (23); that study yielded promising results that have since then been confirmed by larger trials (35); larger randomized controlled trials together with meta-analyses are required to determine the specific effects of sarilumab administration in patients with COVID-19 and to determine whether other contemporary therapies, such as dexamethasone, may lead to improvements in outcomes.

In conclusion, the present study demonstrates that sarilumab is a safe drug with good clinical outcomes in patients with COVID-19 and, hence, may be an alternative regimen for the treatment of patients with SARS-CoV2 severe pulmonary involvement. Further prospective and well-designed clinical studies with larger sample sizes and long-term follow up are warranted to assess the efficacy and the safety of this therapeutic approach to achieve improved outcomes of patients with COVID-19.

**Acknowledgements**

The authors would like to thank Dr Pietro Leanza, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy, for his kind English revision of the manuscript.

**Funding**

No funding was received.

**Availability of data and materials**

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

**Authors' contributions**

All authors (AMa, EC, MC, LL, CB, CM, AMu, BMC, GN and BC) contributed to the study conception and design. AM wrote the manuscript. EC, MC, CB, CM revised the literature and searched for relevant references. LL and MC provided clinical assistance to the patients. AMu was responsible for the laboratory tests and pharmacological treatments. BMC, GN and BC revised the manuscript. GN and BC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Informed consent was obtained from all individual participants included in the present case report study.

**Patient consent for publication**

Written informed consent was obtained from all the patients for publication of the present care report study and accompanying images.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, *et al*: A novel coronavirus from patients with pneumonia in China, 2019. N. Engl J Med 382: 727-733, 2020.
2. Horton R: Offline: COVID-19 is not a pandemic. Lancet 396: 935, 2020.
3. Musumeci G: Effects of COVID-19 Syndemic on Sport Community. J Funct Morphol Kinesiol 7: 19, 2022.
4. Ministero della Salute. Covid-19, situation in Italy. https://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?area=nuovoCoronavirus&id=5367&lingua=english&menu=vuoto. Accessed February 24, 2022.
5. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, Monneret G, Venet F, Bauer M, Brunkhorst FM, *et al*: The COVID-19 puzzle: Deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med 9: 622-642, 2021.
6. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, Laffey J, Carrafiello G, Carsana L, Rizzuto C, *et al*: Pathophysiology of COVID-19-associated acute respiratory distress syndrome: A multicentre prospective observational study. Lancet Respir Med 8: 1201-1208, 2020.
7. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, *et al*: Dexamethasone in Hospitalized patients with Covid-19. N Engl J Med 384: 693-704, 2021.
8. Nissen CB, Sciascia S, de Andrade D, Atsumi T, Bruce IN, Cron RQ, Hendricks O, Roccatello D, Stach K, Trunfio M, *et al*: The role of antirheumatics in patients with COVID-19. Lancet Rheumatol 3: e447-e459, 2021.
9. Angriman F, Ferreyro BL, Burry L, Fan E, Ferguson ND, Husain S, Keshavjee SH, Lupia E, Munshi L, Renzi S, *et al*: Interleukin-6 receptor blockade in patients with COVID-19: Placing clinical trials into context. Lancet Respir Med 9: 655-664, 2021.
10. Bhimraj A, Morgan R, Shumaker A, Lavergne V, Baden L, Cheng VC-C, Edwards KM, Gandhi R, Gallagher J, Muller WJ, *et al*: IDSA Guidelines on the treatment and management of patients with COVID-19. Published by IDSA on 4/11/2020. Last updated, 3/23/2022. Available: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
11. Bassetti M, Giacobbe DR, Bruzzi P, Barisione E, Centanni S, Castaldo N, Corcione S, De Rosa FG, Di Marco F, Gori A, *et al*: Clinical management of adult patients with COVID-19 outside intensive care units: Guidelines from the Italian society of anti-infective therapy (SITA) and the Italian Society of Pulmonology (SIP). Infect Dis Ther 10: 1837-1885, 2021.

12. Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, Patel N and Hagino O; Sarilumab COVID-19 Global Study Group: Sarilumab in patients admitted to hospital with severe or critical COVID-19: A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 9: 522-532, 2021.
13. Zizzo G, Tamburello A, Castelnovo L, Laria A, Mumoli N, Faggioli PM, Stefani I and Mazzone A: Immunotherapy of COVID-19: Inside and beyond IL-6 signalling. Front Immunol 13: 795315, 2022.
14. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Gallagher J, Muller WJ, *et al*: Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis: Apr 27, 2020 (Epub ahead of print). doi: 10.1093/cid/ciaa478.
15. Nunnari G, Sanfilippo C, Castrogiovanni P, Imbesi R, Li Volti G, Barbagallo I, Musumeci G and Di Rosa M: Network perturbation analysis in human bronchial epithelial cells following SARS-CoV2 infection. Exp Cell Res 395: 112204, 2020.
16. Que Y, Hu C, Wan K, Hu P, Wang R, Luo J, Li T, Ping R, Hu Q, Sun Y, *et al*: Cytokine release syndrome in COVID-19: A major mechanism of morbidity and mortality. Int Rev Immunol 41: 217-230, 2022.
17. Cosentino F, Moscatt V, Marino A, Pampaloni A, Scuderi D, Ceccarelli M, Benanti F, Gussio M, Larocca L, Boscia V, *et al*: Clinical characteristics and predictors of death among hospitalized patients infected with SARS-CoV-2 in Sicily, Italy: A retrospective observational study. Biomed Rep 16: 34, 2022.
18. Della-Torre E, Campochiaro C, Cavalli G, De Luca G, Napolitano A, La Marca S, Boffini N, Da Prat V, Di Terlizzi G, Lanzillotta M, *et al*: Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: An open-label cohort study. Ann Rheum Dis 79: 1277-1285, 2020.
19. Gremese E, Cingolani A, Bosello SL, Alivernini S, Tolusso B, Perniola S, Landi F, Pompili M, Murri R, Santoliquido A, *et al*: Sarilumab use in severe SARS-CoV-2 pneumonia. EClinicalMedicine 27: 100553, 2020.
20. Benucci M, Giannasi G, Cecchini P, Gobbi FL, Damiani A, Grossi V, Infantino M and Manfredi M: COVID-19 pneumonia treated with Sarilumab: A clinical series of eight patients. J Med Virol 92: 2368-2370, 2020.
21. REMAP-CAP Investigators; Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, *et al*: Interleukin-6 receptor antagonists in Critically Ill patients with Covid-19. N Engl J Med 384: 1491-1502, 2021.
22. CORIMUNO-19 Collaborative group: Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial. Lancet Rheumatol 4: e24-e32, 2022.
23. Marino A, Pampaloni A, Scuderi D, Cosentino F, Moscatt V, Ceccarelli M, Gussio M, Celesia BM, Bruno R, Borraccino S, *et al*: High-flow nasal cannula oxygenation and tocilizumab administration in patients critically ill with COVID-19: A report of three cases and a literature review. World Acad Sci J 2: 1, 2020.
24. Ceccarelli M, Marino A, Cosentino F, Moscatt V, Celesia BM, Gussio M, Bruno R, Rullo EV, Nunnari G and Cacopardo BS: Post-infectious ST elevation myocardial infarction following a COVID-19 infection: A case report. Biomed Rep 16: 10, 2022.
25. Marino A, Cosentino F, Ceccarelli M, Moscatt V, Pampaloni A, Scuderi D, D'Andrea F, Rullo EV, Nunnari G, Benanti F, *et al*: Entecavir resistance in a patient with treatment-naïve HBV: A case report. Mol Clin Oncol 14: 113, 2021.
26. Celesia BM, Marino A, Borracino S, Arcadipane AF, Pantò G, Gussio M, Coniglio S, Pennisi A, Cacopardo B and Panarello G: Successful extracorporeal membrane oxygenation treatment in an acquired immune deficiency syndrome (AIDS) patient with acute respiratory distress syndrome (ARDS) complicating pneumocystis jirovecii pneumonia: A challenging case. Am J Case Rep 21: e919570, 2020.
27. Celesia BM, Marino A, Del Vecchio RF, Bruno R, Palermo F, Gussio M, Nunnari G and Cacopardo B: Is it safe and cost saving to defer the $CD4^+$ cell count monitoring in stable patients on ART with more than 350 or 500 cells/$\mu$l? Mediterr J Hematol Infect Dis 11: e2019063, 2019.
28. Marino A, Zafarana G, Ceccarelli M, Cosentino F, Moscatt V, Bruno G, Bruno R, Benanti F, Cacopardo B and Celesia BM: Immunological and clinical impact of DAA-mediated HCV eradication in a cohort of HIV/HCV Coinfected patients: Monocentric Italian experience. Diagnostics 11: 2336, 2021.
29. Micali C, Russotto Y, Caci G, Ceccarelli M, Marino A, Celesia BM, Pellicanò GF, Nunnari G and Venanzi Rullo E: Loco-regional treatments for hepatocellular carcinoma in people living with HIV. Infect Dis Rep 14: 43-55, 2022.
30. Marino A, Scuderi D, Locatelli ME, Gentile A, Pampaloni A, Cosentino F, Ceccarelli M, Celesia BM, Benanti F, Nunnari G, *et al*: Modification of serum brain-derived neurotrophic factor levels following anti-HCV therapy with direct antiviral agents: A new marker of neurocognitive disorders. Hepat Mon 20: e95101, 2020.
31. Burgaletto C, Brunetti O, Munafò A, Bernardini R, Silvestris N, Cantarella G and Argentiero A: Lights and shadows on managing immune checkpoint inhibitors in oncology during the COVID-19 Era. Cancers 13: 1906, 2021.
32. Marino A, Munafò A, Zagami A, Ceccarelli M, Di Mauro R, Cantarella G, Bernardini R, Nunnari G and Cacopardo B: Ampicillin plus ceftriaxone regimen against *Enterococcus faecalis* endocarditis: A literature review. J Clin Med 10: 4594, 2021.
33. Erdem H, Hargreaves S, Ankarali H, Caskurlu H, Ceviker SA, Bahar-Kacmaz A, Meric-Koc M, Altindis M, Yildiz-Kirazaldi Y, Kizilates F, *et al*: Managing adult patients with infectious diseases in emergency departments: International ID-IRI study. J Chemother 33: 302-318, 2021.
34. El-Sokkary R, Uysal S, Erdem H, Kullar R, Pekok AU, Amer F, Grgić S, Carevic B, El-Kholy A, Liskova A, *et al*: Profiles of multidrug-resistant organisms among patients with bacteremia in intensive care units: An international ID-IRI survey. Eur J Clin Microbiol Infect Dis 40: 2323-2334, 2021.
35. RECOVERY Collaborative Group: Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 397: 1637-1645, 2021.