Safety and Efficacy of Tocilizumab in the Treatment of Severe Acute Respiratory Syndrome Coronavirus-2 Pneumonia: A Retrospective Cohort Study

Atul Patel  
*University of South Florida, akpatel4@mail.usf.edu*

Kinjal Shah  
*Department of Infectious Diseases, Sterling Hospital, Ahmedabad, Gujarat, India*

Mitkumar Dharsandiya  
*Department of Infectious Diseases, Sterling Hospital, Ahmedabad, Gujarat, India*

Ketan Patel  
*Department of Infectious Diseases, Sterling Hospital, Ahmedabad, Gujarat, India*

Tushar Patel  
*Department of Pulmonary and Critical Care Medicine, Sterling Hospital, Ahmedabad, Gujarat, India*

Follow this and additional works at: [https://scholarcommons.usf.edu/usf_fcrc_all](https://scholarcommons.usf.edu/usf_fcrc_all)

Part of the [Medicine and Health Sciences Commons](https://scholarcommons.usf.edu)

_Scholar Commons Citation_  
Patel, Atul; Shah, Kinjal; Dharsandiya, Mitkumar; Patel, Ketan; Patel, Tushar; Patel, Mukesh; Reljic, Tea; and Kumar, Ambuj. "Safety and Efficacy of Tocilizumab in the Treatment of Severe Acute Respiratory Syndrome Coronavirus-2 Pneumonia: A Retrospective Cohort Study" (2020). *USF Libraries Florida COVID Research Collection publications*. 10.  
[https://scholarcommons.usf.edu/usf_fcrc_all/10](https://scholarcommons.usf.edu/usf_fcrc_all/10)

This Article is brought to you for free and open access by the USF Libraries Florida COVID-19 Research Collection at Scholar Commons. It has been accepted for inclusion in USF Libraries Florida COVID Research Collection publications by an authorized administrator of Scholar Commons. For more information, please contact scholarcommons@usf.edu.
Authors
Atul Patel, Kinjal Shah, Mitkumar Dharsandiya, Ketan Patel, Tushar Patel, Mukesh Patel, Tea Reljic, and Ambuj Kumar

This article is available at Scholar Commons: https://scholarcommons.usf.edu/usf_fcrc_all/10
Abstract

Background: Cytokine release storm (CRS) in severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) is thought to be the cause for organ damage and death which is independent of the actual viral burden. Tocilizumab (TCZ), an interleukin-6 receptor antagonist, is approved for the treatment of CRS. We describe the efficacy and safety of TCZ in SARS CoV-2 pneumonia. Methods: This retrospective study was conducted at a tertiary care hospital from April 20 2020 to May 21 2020. The primary endpoint was the cumulative incidence of a composite of either need for admission to the intensive care unit (ICU) with invasive mechanical ventilation or death. Safety outcomes included an increase in liver transaminases and/or evidence of infection. Results: A total of 20 patients received TCZ during the study period. The median age was 54 years (95% confidence interval [CI] 47–63). About 85% of the patients were male. Nearly 70% of the patients had at least one comorbidity. About 55% required ICU admission. The median duration of ICU stay was 11 days (95% CI: 3–13 days). The cumulative incidence of the requirement for mechanical ventilation, clinical improvement and mortality was 11% (95% CI: 0.03%–1%), 74% (95% CI 37%–89%) and 25% (95% CI: 11%–63%), respectively. There was no difference in outcomes according to age, gender or computed tomography severity score. Asymptomatic transaminitis was the most common drug reaction (55%), and one patient developed bacteraemia. Conclusions: TCZ is likely a safe and effective modality of treatment for improving clinical and laboratory parameters of SARS CoV-2 patients with a reduction in ICU stay and ventilatory care need.

Keywords: Coronavirus, COVID-19, cytokine release storm, severe acute respiratory syndrome coronavirus-2, tocilizumab

Introduction

India reported the first case of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) in January 2020. Since then, the number of positive cases has been increasing. As of 5 June 2020, more than 380,000 patients globally and 6300 people in India have died mainly due to bilateral pneumonia, respiratory failure and thrombotic complications attributed to immune-mediated inflammatory damage in SARS CoV-2 infection. SARS-CoV-2 and other viruses in the corona family (SARS CoV-1 and Middle East respiratory syndrome) infection induce a hyperinflammatory response resembling cytokine release storm (CRS) with secondary haemophagocytic lymphohistiocytosis or macrophage-activation syndrome (MAS), with markedly elevated pro-inflammatory interleukins (IL-1β and IL-6) and tumour necrosis factor.[1,2] Increased IL-6 blood level was identified as one of the laboratory markers associated with high mortality in the study by Zhou et al.[3] An overreacting immune system to viral infections including coronaviruses and influenza with CRS is thought to be the cause for elevated pro-inflammatory interleukins (IL-1β and IL-6) and tumour necrosis factor.[1,2] Increased IL-6 blood level was identified as one of the laboratory markers associated with high mortality in the study by Zhou et al.[3] An overreacting immune system to viral infections including coronaviruses and influenza with CRS is thought to be the cause for
pulmonary and other organ damage and dysfunction leading to death which is independent of the actual viral burden and is usually seen following the acute phase of the disease. Researchers have used antiviral agents for controlling viral replication and found them to be beneficial when administered early, but once CRS has established, they seem to have little role. In the absence of specific effective treatment to prevent progression of respiratory symptoms in patients with SARS CoV-2 pneumonia, researchers have tried different monoclonal antibodies to block IL-1 and IL-6 receptor for the management of CRS with some success. IL-6 receptor antagonist, tocilizumab (TCZ), is the most common agent used for treatment of SARS CoV-2 pneumonia with evidence of CRS followed by anakinra in China, France and Italy and it has shown a survival benefit in these patients.

In this study, we describe the efficacy and safety of TCZ in a group of patients with moderate and severe SARS CoV-2 disease.

**METHODS**

**Settings and inclusion criteria**

We performed a retrospective study at a tertiary care hospital in Western India. The study was approved by the Sterling Hospital Ethics Committee with reference number SH-CR/EC/AP/Academic/180–2020, dated 27 May 2020. All consecutive adult patients (>18 years) treated with TCZ between 21 April 2020 and 20 May 2020 for CRS associated with SARS CoV-2 pneumonia were eligible for inclusion.

The decision to administer TCZ was based on the presence of any or all three of the following: SpO2 of ≤94%, laboratory indication of CRS as indicated by C-reactive protein (CRP) >10 times of (ULN) or double in the last 24 h, D-dimer >2500 ng/ml, worsening respiratory status or persistent high-grade fever.

TCZ was not considered in patients with active tuberculosis (TB), current or past exposure to TB or laboratory confirmed evidence of bacterial infection, serum glutamic pyruvic transaminase (SGPT) >5 times of ULN, absolute neutrophil count <1000 and platelets <50,000.

**Treatment protocol**

Patient received 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose of 800 mg. Up to 1 additional dose was administered if clinical symptoms worsened or showed no improvement. All patients received the standard of care according to the current treatment protocol recommended by the Ministry of Health and Family Welfare in the state of Gujarat along with other necessary supportive measures. These included oral hydroxychloroquine 400 mg/day for 5 days after a loading dose of 400 mg twice a day on 1st day, oral azithromycin 500 mg/day for 5 days and IV ceftriaxone 1 g per day for 5 days. Antiocoagulation with low-molecular-weight heparin or unfractionated heparin infusion was used if patient’s D-dimer was >1000 ng/ml. Some patients also received single dose of 80 mg IV methylprednisolone before receiving TCZ.

**Definitions**

**Mild infection**

SARS CoV-2 patients have mild infections such as fever, myalgia, body pain, loss of taste, smell without radiological evidence of pneumonia and maintaining saturation on room air >94%.

**Moderate disease**

Moderate diseases are observed in patients with hypoxia with SpO2 <94 and complaining of shortness of breath with radiological evidence of pneumonia.

**Severe disease**

Severe disease includes all of the above (as in moderate

**Table 1: Baseline characteristics of study patients**

| Characteristics                  | Number of subjects | n (%) / Median and 95% CI |
|---------------------------------|--------------------|--------------------------|
| Age (years)                     | 20                 | 54 (47-63)               |
| Sex                             | 20                 | Male 17 (85%) Female 3 (15%) |
| Comorbidities                   |                    |                          |
| Diabetes                        | 20                 | 10 (50%)                 |
| Hypertension                    | 20                 | 10 (50%)                 |
| Ischemic heart disease          | 20                 | 4 (20%)                  |
| Parkinsonism                    | 20                 | 1 (5%)                   |
| Hepatitis B                     | 20                 | 1 (5%)                   |
| Symptoms                        |                    |                          |
| Fever                           | 20                 | 17 (85%)                 |
| Cough                           | 20                 | 12 (60%)                 |
| Shortness of breath             | 20                 | 10 (50%)                 |
| Diarrhea                        | 20                 | 2 (10%)                  |
| Throat pain                     | 20                 | 2 (10%)                  |
| Anosmia                         | 20                 | 2 (10%)                  |
| Loss of taste                   | 20                 | 1 (5%)                   |
| Body pain                       | 20                 | 1 (5%)                   |
| Myalgia                         | 20                 | 1 (5%)                   |
| Symptoms day at the time of admission days | 20 | 8 (2-14) |
| CT severity score               | 16                 | 11.06 (7-13)             |
| Tocilizumab administered on day of Symptoms | 20 | 9.5 (8-10) |
| Other Treatments                |                    |                          |
| Hydroxychloroquine              | 20                 | 19 (95%)                 |
| One dose of Methyl Prednisolone | 20                 | 13 (65%)                 |
| Low Molecular weight Heparin    | 20                 | 20 (100%)                |
| Aspirin                         | 20                 | 17 (85%)                 |
| Baseline Oxygen Requirement     |                    |                          |
| Ambient air                     | 20                 | 4 (20%)                  |
| Nasal Prongs                    | 20                 | 3 (15%)                  |
| Face mask                       | 20                 | 3 (15%)                  |
| Non rebreathing mask            | 20                 | 3 (15%)                  |
| Noninvasive ventilator/HFNC     | 20                 | 7 (35%)                  |
Table 2: Change in laboratory parameters after tocilizumab

| Laboratory parameters (normal range) | Number of patients | Mean (95% Confidence intervals) | P       |
|-------------------------------------|--------------------|---------------------------------|---------|
|                                     |                    | Baseline                        | Day 3   | Day 7   | Baseline versus day 3 | Baseline versus day 7 | Day 3 versus day 7 |
| Neutrophil-Lymphocyte Ratio (1 - 3)| 20                 | 7.45 (5.17-9.73)                | 8.13 (3.01-13.25) | 5.19 (2.30-8.06) | 0.51 | 0.03 | 0.11 |
| C-reactive protein mg/dL (<1 mg/dL)| 20                 | 17.2 (12.65-21.75)              | 2.59 (2.04-3.14) | 0.28 (0.1-0.45) | 0.0001 | 0.0004 | 0.0005 |
| Serum Ferritin (21-274 ng/ml)      | 20                 | 1020.35 (501.78-1538.92)        | 1289.22 (264.82-2313.62) | 917.94 (128.30-1705.59) | 0.96 | 0.07 | 0.02 |
| D-dimer (0- 500ng/ml)              | 19                 | 1613.7 (588.55-2668.92)         | 2791.22 (1064.92-4517.53) | 3529.35 (1625.72-5432.98) | 0.31 | 0.29 | 0.22 |
| Serum glutamic-pyruvic transaminase (5-49 IU/L) | 20 | 43.55 (32.56-54.54) | 81.22 (46.12-116.32) | 114.0 (61.61-166.38) | 0.002 | 0.005 | 0.23 |

disease) and requiring high-flow nasal cannula or ventilatory assistance.

Outcomes
The primary endpoint was the cumulative incidence of a composite of either need for admission to the intensive care unit (ICU) with invasive mechanical ventilation or death.

The secondary endpoints were duration of ICU stay, time to hospital discharge, change in the neutrophil–lymphocyte ratio (NLR), CRP, D-dimer and serum ferritin after TCZ administration. Safety outcomes included an increase in liver aminotransferase enzymes (more than three times the upper limit of normal) and documented evidence of bacterial or fungal infection.

Data abstraction
Information on patient demographics, laboratory and radiology parameters were extracted from medical records and entered into an electronic database. Data were retrieved on patient demographics and medical characteristics including age, sex, presenting clinical symptoms, comorbidities (e.g., hypertension, diabetes and ischemic heart disease), radiological assessment, computed tomography (CT) severity score, relevant laboratory parameters performed during hospitalisation including NLR, CRP, SGPT, serum ferritin and D-dimer and outcomes were derived at from the medical charts. Clinical response was assessed using the World Health Organisation Modified Ordinal Scale for need for oxygen requirement. Scale 1 denotes patients not hospitalised or discharged; 2 denotes patients maintaining oxygen saturation on room air; 3 denotes patients requiring oxygen supplements with the following subgroups: 3a means nasal prong, 3b means simple mask and 3c means non-rebreathing mask; 4 denotes patients with high-flow nasal oxygen therapy, non-invasive mechanical ventilation or both; 5 denotes patients requiring invasive mechanical ventilation, ECMO or both and 6 denotes death.

Statistical analysis
Demographic and patient characteristics were described using descriptive statistics where categorical variables were summarised as rates or per cent and continuous variables as median along with 95% confidence intervals (CIs). The change in continuous variables across the time point was assessed using the paired non-parametric Wilcoxon Signed-Rank Test. The time-to-event outcomes were analysed using Kaplan–Meier analysis and summarised as proportions along with 95% CI. All analyses were performed using the NCSS 2020 Statistical Software (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

RESULTS
Patient characteristics
Between March 21 and May 20 2020, 65 confirmed SARS CoV-2 patients were hospitalised at the tertiary care private sector hospital. Of the hospitalised patients, 33 required supportive care only as they were either asymptomatic or mildly symptomatic. Twelve patients with moderate-to-severe disease with pneumonia and hypoxia received only corticosteroids, while 20 patients received TCZ for their moderate and severe SARS CoV-2 disease and were included in the study Baseline demographic features of patients who received TCZ are shown in Table 1, the median age was 54 years (95% CI: 47–63). Eighty-five per cent of patients (n = 17) were male and 15% were female (n = 3). The most common presenting symptoms were fever (85%; n = 17) and cough (60%; n = 12), followed by shortness of breath (50%; n = 10). Fifteen per cent (n = 3) of patients presented with all three symptoms of fever, cough and shortness of breath. Other presenting symptoms were body pain, diarrhoea, loss of taste, headache, sore throat, myalgia and back pain (n = 1). The median CT severity score was 10.5 (95% CI: 7–13). Fifty per cent of patients (n = 10) had diabetes and hypertension and 20% (n = 4) had ischemic heart disease. Seventy per cent of patients (n = 14) had at least one comorbidity of diabetes, hypertension or ischemic heart disease.

Baseline status and treatment characteristics
The median number of days patients who were symptomatic for SARS CoV-2 at the time of hospitalisation was 8 (95% CI: 118
5–10 days). Ninety-five per cent of patients (n = 19) received hydroxychloroquine. All patients received a combination antibiotic regimen of either azithromycin and ceftriaxone (65%; n = 13) or azithromycin and meropenem (5%; n = 1) or azithromycin alone (30%; n = 6). In addition, 65% of the patients (n = 13) also received at least one dose of corticosteroids before TCZ. The choice of corticosteroids was either methyl prednisone, dexamethasone or hydrocortisone. Steroids were discontinued in all patients once the patient received TCZ. All the patients received anticoagulation with either low-molecular-weight heparin alone (15%; n = 3) or in combination with aspirin (85%; n = 17). The median time to TCZ administration was 9.5 days (95% CI: 8–10 days) from symptom onset.

At baseline, 20% (n = 4) of patients were on ambient air, followed by nasal prong (15%; n = 3), mask (15%; n = 3), non-rebreather mask (NRBM; 15%; n = 3) and non-invasive positive air ventilation (35%; n = 7), respectively. The progression and outcome of patients throughout the hospital stay is illustrated in Figure 1. The median time to follow-up from the day of illness was 12 days (95% CI: 9–16 days).

**Outcomes**

Of all the admitted patients, 55% (n = 11) (8 were admitted in the ICU, while 3 were shifted from the ward to the ICU) required ICU admission. The median duration of ICU stay was 11 days (95% CI: 3–13 days). As shown in Figure 2a, the cumulative incidence of requirement for mechanical ventilation was 11% (95% CI: 0.03%–41%). The first patient required ventilation on day 4 of admission and the second patient on day 5 of admission. The cumulative incidence of clinical improvement was 74% [95% CI: 37%–89%; Figure 2b]. The
cumulative incidence of mortality was 25% [95% CI: 11%–63%; Figure 2c]. The mean time to clinical improvement and mortality was 24 days (95% CI: 19–29 days). There was no difference in outcomes according to the age, gender or CT severity score. All patients, who had high-grade fever became afebrile within 24 h of TCZ. This clinical benefit was the most striking and rapid.

The change in laboratory parameters after TCZ is described in Table 2 (day 0 is the day of TCZ administration).

**Neutrophil–lymphocyte ratio**
The mean NLR was 7.45 (95% CI 5.17–9.73) on day zero, 8.13 (95% CI 3.01–9.73) on day 3 and 5.19 (95% CI 2.3–8.06) on day seven. The change in NLR levels from day 0 to day 7 was statistically significant ($P = 0.03$) but not for day 3 versus day 7 ($P = 0.11$).

**C-reactive protein test**
The mean CRP was 17.2 (95% CI 12.65–21.75) on day 0, 2.59 (95% CI 2.04–3.14) on day 3 and 0.28 (95% CI: 0.1–0.45) on day 7. The change in CRP values was statistically significant from day 0 to day 3 ($P = 0.0001$) and day 7 ($P = 0.0004$) and between day 3 and day 7 ($P = 0.0005$).

**Serum ferritin**
The mean serum ferritin was 1020.35 (95% CI: 501.78–1538.92) on day 0, 1289.22 (95% CI: 264.82–2313.62) on day 3 and 917.94 (95% CI: 128.3–1705.59) on day 7. The change in serum ferritin levels from day 0 to day 3 ($P = 0.96$) and day 7 ($P = 0.07$) was not statistically significant. The change in serum ferritin levels from day 3 to day 7 was statistically significant ($P = 0.02$).

**D-Dimer**
The mean D-dimer was 1613.7 (95% CI: 588.55–2668.92) on day 0, 2791.22 (95% CI: 1064.92–4517.53) on day 3 and 3529.35 (95% CI: 1625.72–5432.98) on day 7. The change in D-dimer values from day 0 to day 3 ($P = 0.31$) and day 7 ($P = 0.29$) or from day 3 to day 7 ($P = 0.22$) was not statistically significant.

**Serum glutamic-pyruvic transaminase**
The mean SGPT was 43.55 (95% CI: 32.56–54.54) on day 0, 81.22 (95% CI: 46.12–116.32) on day 3 ($P = 0.002$) and 114 (95% CI 61.61–166.38) on day 7. The change in SGPT levels from day 0 to day 3 ($P = 0.002$) and day 7 ($P = 0.005$) was statistically significant. The change in SGPT levels from day 3 to day 7 was not statistically significant ($P = 0.23$).

**Changes in radiological assessment**
At baseline, 16 patients had CT scan of the thorax and 4 patients had X-ray of the chest. Follow-up CT scan was not performed to assess radiological improvement. X-ray of the chest was carried out in all patients before discharge which showed resolution. Figure 3 shows the X-ray of the chest at the time of TCZ, after 1 week and at the time of discharge of patient numbers 12 and 17 who stayed in hospital for 20 and 22 days, respectively, showing initial worsening followed by improvement.

Overall, the TCZ injection was well tolerated, and none of the patients had an infusion-related adverse drug events. Asymptomatic transaminitis was seen in 11 (55%) patients following TCZ and one patient had 8 times of ULN of SGPT. One patient had transient leukopenia and neutropenia and one
We suggest that timely use of TCZ as determined by fever, worsening hypoxia, high CRP and D-dimer in patients with SARS CoV-2 pneumonia can be a lifesaving. Notably, previous published studies with the use of TCZ in SARS CoV-2 have shown survival benefit with marked reduction in inflammatory markers. The results from one non randomised study also reported benefit with the use of a single low dose of tocilizumab, in patients with severe SARS CoV-2 pneumonia with significantly higher survival rates in treated patients compared to patients who did not receive Tocilizumab. In addition, the positive treatment effect on survival with TCZ was independent from clinical comorbidities associated with poor outcomes such as age, diabetes, hypertension or heart diseases. This study also reported no infections in the TCZ group.

A major limitation of our study is the lack of a comparator arm which was not possible in this acute setting due to unavailability of other regimen justifying equipoise without putting patients at additional risk for receiving any inferior treatment. Furthermore, given the life-threatening nature of the disease characterised by sudden worsening and rapid progression over few hours, a comparative arm cannot be justified. As the new treatments evolve over time, a randomised clinical trial in the future will be able to provide reliable evidence on the actual therapeutic benefit associated with the use of TCZ in CRS in SARS CoV-2. Until then, these findings validate the use of TCZ for the management of CRS in SARS CoV-2 safely.

In summary, TCZ effectively improves clinical and laboratory parameters with a reduction in the need for ICU and ventilatory care in patients with moderate-to-severe SARS CoV-2 disease.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
2. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: Interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020;55:105954.
3. 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.
4. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;39:529-39.
5. Kumar A. Early versus late oseltamivir treatment in severely ill patients with 2009 pandemic influenza A (H1N1): Speed is life. J Antimicrob Chemother 2011;66:959-63.
6. Hiba V, Chowers M, Levi-Vinograd I, Rubinovitch B, Leibovici L, Paul M. Benefit of early treatment with oseltamivir in hospitalised patients with documented 2009 influenza A (H1N1): Retrospective cohort study. J Antimicrob Chemother 2011;66:1150-5.
7. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M.
Patel, et al.: Tocilizumab in SARS-CoV-2 pneumonia

Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: A retrospective cohort study. Lancet Infect Dis 2014;14:1090-5.

8. Alzghari SK, Acuña VS. Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. J Clin Virol 2020;127:104380.

9. van Kraaij TD, Mostard RL, Ramiro S, Magro Checa C, van Dongen CM, van Haren EH, et al. Tocilizumab in severe COVID-19 pneumonia and concomitant cytokine release syndrome. Eur J Case Rep Intern Med 2020;7:001675.

10. Aouba A, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series Annals of the Rheumatic Diseases Published Online First: 06 May 2020. doi: 10.1136/ annrheumdis-2020-217706.

11. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. The Lancet Rheumatology 2020;0:e393–400.https://doi.org/10.1016/ S2665-9913(20)30164-8.

12. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.

13. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early short course corticosteroids in hospitalized patients with COVID-19. Clinical Infectious Diseases, ciaa601, https://doi.org/10.1093/cid/ciaa601.

14. Dimopoulos G, de Mast Q, Markou N, Theodorakopoulou M, Konnos A, Moktaroudi M, et al. Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. Cell Host Microbe 2020;28:117-23.e1. doi:10.1016/j.chom.2020.05.007.

15. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med 2020;76:31-5.

16. Michot JM, Albiges L, Chaput N, Saada V, Pommeret F, Griscelli F, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: A case report. Ann Oncol 2020;31:961-4.

17. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020;117:10970-5.

18. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020;19:102568.