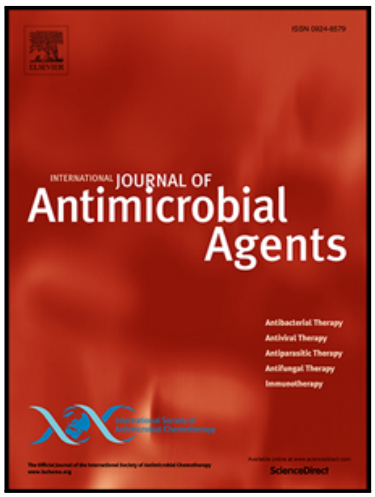
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Tocilizumab administration in a refractory case of COVID-19

Farzaneh Dastan , Seyed Alireza Nadji , Ali Saffaei , Payam Tabarsi

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Highlights

- Pathophysiological studies have demonstrated the role of inflammatory mediators in COVID-19 pneumonia
- In some COVID-19 cases, especially those with impaired immune function, an uncontrolled immune response that triggers an overproduction of immune cells and their signaling molecules occurs.
- Cytokine release syndrome may be the underlying pathophysiology of refractory cases.
- Tocilizumab as an IL-6 antagonist may have a promising role in cytokine release syndrome which occurs in COVID-19.
- However, while tocilizumab is a promising agent against COVID-19, it is not an appropriate agent in patients with active or latent tuberculosis, bacterial and fungal infections, multi-organ failure, and gastrointestinal perforation.
- Clinicians should be aware of the precautions and contraindications of tocilizumab.

Tocilizumab administration in a refractory case of COVID-19

Farzaneh Dastan[a,b], Seyed Alireza Nadji[c], Ali Saffaei[d], Payam Tabarsi[e,*], tabarsi@nritld.ac.ir, payamtabarsi@yahoo.com

[a]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[b]Chronic Respiratory Diseases Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[c]Virology Research Center, National institutes of Tuberculosis and Lung diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[d]Student Research Committee, Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[e]Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*]Corresponding author: Prof. Payam Tabarsi, Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Daarabad St, Niyavaran St, Tehran, Iran.

Telefax: +98 21 2712 3000; Zip Code: 1956944413.

Dear Editor,

On March 2, 2020, a 36-year-old male came to the emergency department of Dr. Masih Daneshvari Hospital in Iran with a 3-day history of fever and dry cough. The patient was a physician with a history of close contact with COVID-19 cases. The patient had no underlying diseases and history of medicine usage. Physical examination revealed a body temperature of 39 °C, blood pressure of 120/70 mmHg, heart rate of 90 beats per minute, and peripheral oxygen saturation of 92%. The patient exhibited no dyspnea. Laboratory results revealed a white blood cell count of 5.81 cells/μL with 29.6% lymphocytes and no other abnormality was seen in his laboratory results. The patient's swab specimen was tested positive for COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) on March 4, 2020 (cycle threshold value 22.39) [1]. Chest X-ray imaging revealed bilateral lower lobe infiltration (Fig. 1a). Hence, the patient was diagnosed with COVID-19 pneumonia. Hydroxychloroquine at dose of 200 mg p.o. twice a day, oseltamivir at dose of 75 mg p.o. twice a day, lopinavir/ritonavir at dose of 200/50 mg p.o. in two tablets twice a day, and interferon β-1a at dose of 12 million units s.c. every other day were administered. On March 8, 2020 the clinical condition of the patient deteriorated, and he exhibited dyspnea with an oxygen saturation of 85%. Fever and cough were persistent, and new chest X-ray imaging revealed progression of bilateral infiltration in the lower and upper lobes (Fig. 1b). We decided to initiate ribavirin at dose of 1200 mg p.o. b.i.d. and intravenous immunoglobulin at a dose of 20 mg i.v. daily. Meropenem and teicoplanin were also started to cover any probable bacterial sources. After 2 days, on March 10, 2020, the clinical condition of the patient worsened. Dyspnea continued with greater severity and an oxygen saturation of 83%. The ratio between the partial pressure of oxygen in arterial blood (PiO_2) and the fraction of inspired oxygen decreased to 103 mmHg. Chest X-ray imaging did not show significant changes compared with the previous images (Fig. 1c), and the patient was a

candidate for intubation and invasive mechanical ventilation but this procedure did not achieve. At this time, tocilizumab was considered as a last chance of therapy. The patient's IL-6 level was checked, and a value of over 200 pg/mL was found. QuantiFERON-TB testing was negative for *Mycobacterium tuberculosis*. Viral markers, including hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, were reported negative. Hence, tocilizumab (Actemra Hoffmann-La Roche Limited), as a single dose of 400 mg was infused for him over 2 hours. The patient's vital signs were checked carefully during infusion to monitor any probable adverse effects. After 2 days, the patient's dyspnea improved gradually and his oxygen saturation increased to 90%. Chest X-ray imaging also showed less infiltration in comparison with previous imaging (Fig. 1d). Recovery was observed over the next few days, and dyspnea and oxygen saturation improved significantly. IL-6 levels were checked and found to decrease from 29 pg/mL to 6 pg/mL within a few days. Lung infiltration remarkably recovered in subsequent chest X-ray imaging (Fig. 1e and Fig. 1f). A swab specimen was tested negative for COVID-19 by RT-PCR on March 18, 2020. After 18 days of hospitalization, the patient was discharged with acceptable clinical condition. No bothersome dyspnea was noted, and oxygen saturation was 93% without supplemental oxygen. The timeline of vital signs, therapeutic regimens, and laboratory results are shown in Fig. 2.

Cytokine release syndrome may be the underlying pathophysiology of refractory cases of COVID-19. Tocilizumab is a recombinant humanized monoclonal antibody developed against soluble and membrane-bound IL-6 receptors. Tocilizumab prevents the binding of IL-6 to its receptors and reduces the activity of the cytokine by competing with both the soluble and membrane-bound forms of its receptors [2]. In the current case, we faced a refractory COVID-19 case who did not respond to conventional therapeutic agents and tocilizumab administered as a salvage therapy. In contrast to hydroxychloroquine, tocilizumab may be a

useful agent in severe cases who have not responded to conventional therapy (chloroquine/hydroxychloroquine and antivirals) and those patients with elevated levels of IL-6 [3]. Successful management of tocilizumab was reported in recent literature. Hammami MB et al., reported COVID-19 in a liver transplant recipient who responded to tocilizumab therapy [4]. The promising role of tocilizumab also reported in pilot studies. Improvement in respiratory and laboratory parameters were observed in those studies [5, 6]. However, while tocilizumab is a promising agent against COVID-19, it is not an appropriate agent in patients with active or latent tuberculosis, bacterial and fungal infections, multi-organ failure, and gastrointestinal perforation [7]. In conclusion, tocilizumab may be considered a salvage therapeutic agent in COVID-19 patients who did not respond to other agents. Clinicians should be aware of the precautions and contraindications of tocilizumab, such as latent infection, and administer the drug with caution.

Declarations

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Competing Interests: None

Ethical Approval: Written informed consent form obtained

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Titles for figures

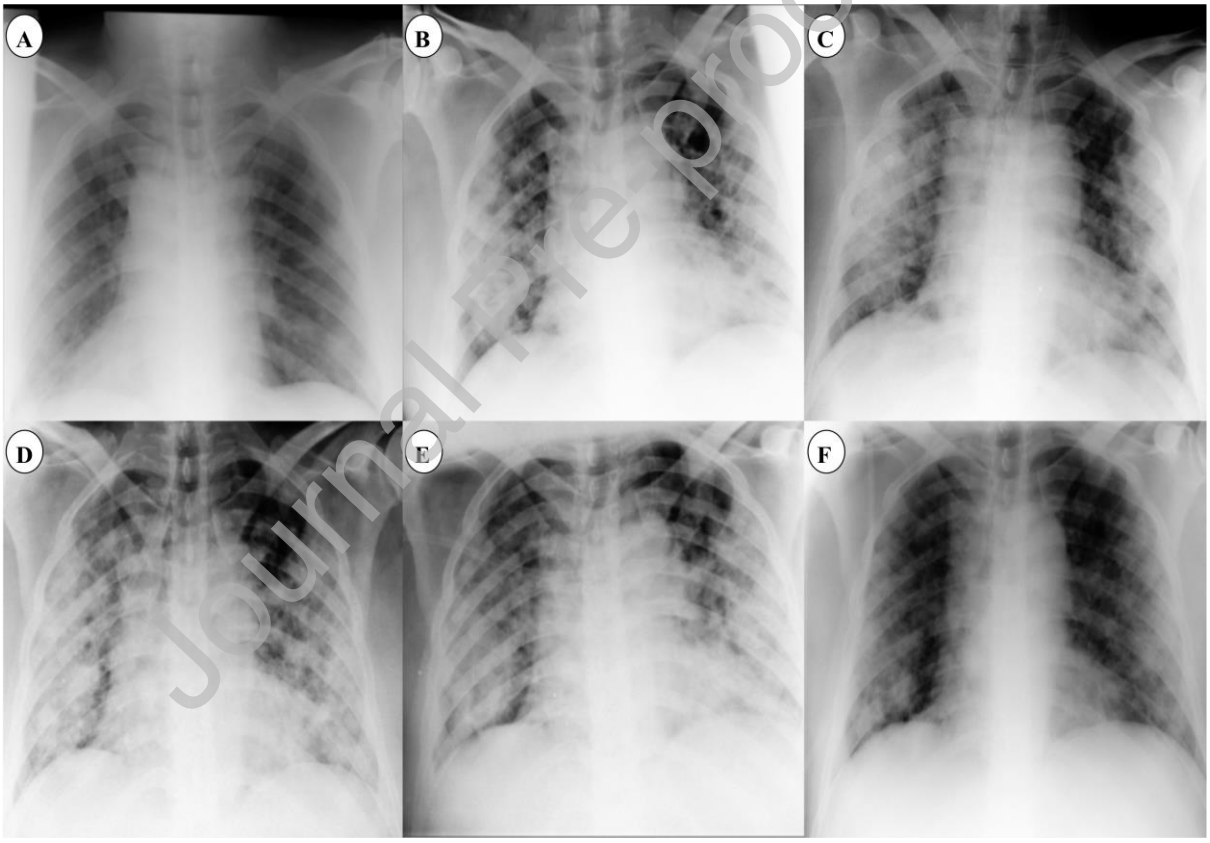

Fig. 1. Chest X-ray of the patient during hospitalization. (a, b, and c) Progression of lower and upper lobe infiltration. (d, e, and f) Recovery of infiltration after tocilizumab administration.

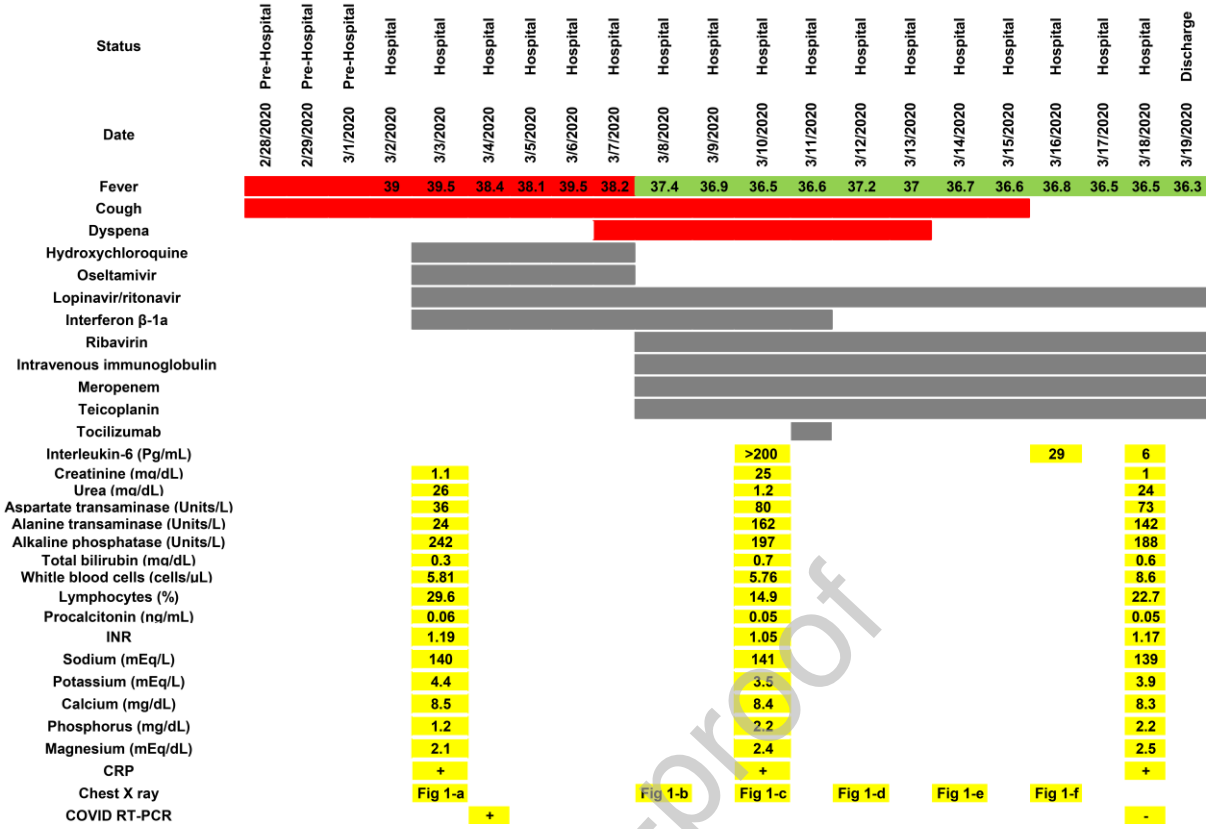

Fig. 2. Timeline of vital signs, therapeutic regimens, and laboratory results during hospitalization.