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Tocilizumab in the treatment of a critical COVID-19 patient: a case report

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Abstract. – In December 2019, Coronavirus disease 2019 (COVID-19) emerged in Wuhan and rapidly spread throughout China and the rest of the world. COVID-19 is currently a global pandemic. There are cytokine storms in severe COVID-19 patients. Interleukin-6 plays an important role in cytokine storm. Tocilizumab is a blocker of interleukin-6 receptor, which is likely to become an effective drug for patients with severe COVID-19. Here, we reported a case in which tocilizumab was effective for a critical COVID-19 patient.

Key Words:
COVID-19, Tocilizumab, Interleukin-6, Cytokine storm.

Introduction

Most patients with Coronavirus disease 2019 (COVID-19) have mild symptoms at the time of onset, but some have rapidly deteriorated clinical symptoms, including shortness of breath, dyspnea, and even respiratory failure, as well as a rapid increase in ground-glass lesions on chest CT. These patients often require a nasal catheter or high-flow nasal cannula (HFNC) supplement and even ventilator-assisted respiration. There is currently no specific treatment for COVID-19. Under the recommended treatment strategies, 4.3-11% of patients may still die[1,2]. If a case progresses to critical illness, the mortality rate may reach 60.5%[3]. A large number of data suggest that there are cytokine storms in severe patients, which are also an important cause of death[4]. Therefore, the treatment of cytokine storm has become an important part of rescuing severe patients. Interleukin (IL)-6 plays an important role in cytokine release syndrome. If it can block the signal transduction pathway of IL-6, it is expected to become a new method for the treatment of severe patients[5].

Case Report

A 57-year-old male who was a taxi driver in Wuhan (China), was admitted to the hospital with chest tightness and fever for 10 days on February 15, 2020. The patient presented chest tightness and fever 10 days previous, and his highest body temperature was 38.5°C, without chills, cough, dyspnea, or diarrhea. He went to see a doctor 1 week prior and underwent chest computed tomography (CT) scans and SARS-CoV-2 nucleic acid testing. His chest CT images at Wuhan No. 5 hospital showed ground-glass opacities involving the subpleural regions of both lungs. His throat swabs were negative for SARS-CoV-2 nucleic acid. His temperature was normal after taking abidol and Lianhua Qingwen capsules for 2 days, but he still felt chest tightness. He did not have a history of going to the Huanan Seafood Market. His wife presented with fever 3 days later. His physical examination revealed a body temperature of 37°C, blood pressure of 120/85 mmHg, pulse of 87 beats per minute,

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respiratory rate of 19 breaths per minute, and oxygen saturation of 94% while breathing ambient air. Lung auscultation revealed rhonchi, the heart rhythm was uniform, and no murmur was heard in each valve area. The shape of the abdomen was normal. There was no tenderness or rebound pain. No edema was observed in either lower limb. Physiological reflexes were present. After admission, the patient received oxygen supplement through a nasal cannula at 3 L/min, his oxygen saturation was 98%, and he continued to take abidol and Lianhua Qingwen capsules (Figure 1). On days 2 through 5 (February 19) of hospitalization, the patient's vital signs remained stable. Laboratory tests showed that his white blood cell (WBC) count, neutrophil count, procalcitonin (PCT), D-dimer, creatinine, urea nitrogen, potassium, and sodium were normal. However, his lymphocyte count (0.44 × 10^9/L) and albumin (26 g/L) were decreased, whereas C-reactive protein (CRP) (84.3 mmol/L) was increased. Chest CT scans revealed ground-glass opacities involving the subpleural regions of both lungs (Figure 2A), and a SARS-CoV-2 nucleic acid test of nasopharyngeal swamp specimens was negative. On hospital day 6, the patient felt shortness of breath after activity, and the flow of nasal cannula oxygen was increased to 5 L/min; oxygen saturation reached 98%, and the shortness of breath was relieved. Liver function results showed that alanine transaminase (ALT) (124 IU/L) and aspartate aminotransferase (AST) (95 IU/L) levels were increased, but albumin (26 g/L) was decreased. The patient received diammonium glycyrrhizinate capsules 150 mg three times per day orally for liver protection and plasbumin infusion to improve hypoproteinemia. On day 9 (February 23), the patient felt shortness of breath again, without cough or chest pain. Blood gas analysis (delivery oxygen 5 L/min by nasal catheter) revealed pH 7.437, PCO_2 32.4 mmHg, PO_2 64 mmHg, HCO_3^- 21.9 mmol, and BE 2 mmol/L. A rapid nucleic acid amplification test for influenza A and B was negative. Retesting of nasopharyngeal swabs for SARS-CoV-2 nucleic acid was negative. The patient received gamma globulin 10 g and methylprednisolone 40 mg per day infusion as well as chlorochloroquine 200 mg twice a day orally. On day 12 (February 26), the patient experienced exacerbated shortness of breath and slight chest pain. Oxygen saturation was only 90%, while delivery oxygen was 5 L/min. Blood gas analysis revealed that PO_2 was 47 mmHg. The patient underwent emergency chest CT, which showed the range of ground-glass opacity extension (Figure 2B) and a small amount of bilateral

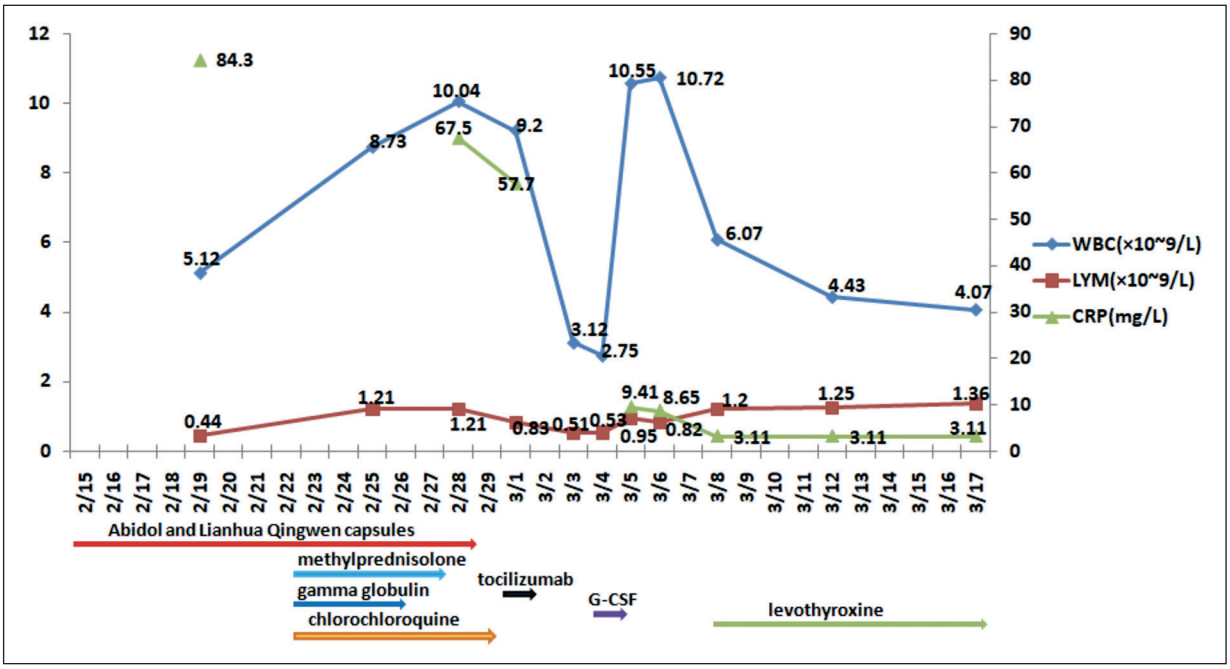

Figure 1. Evolution of WBC count, lymphocyte count, C-reactive protein in blood of patient with COVID-19 before and after tocilizumab, and the treatment strategy after admission. WBC, white blood cell; LYM, lymphocyte; CRP, C-reactive protein; G-CSF, granulocyte-colony stimulating factor.

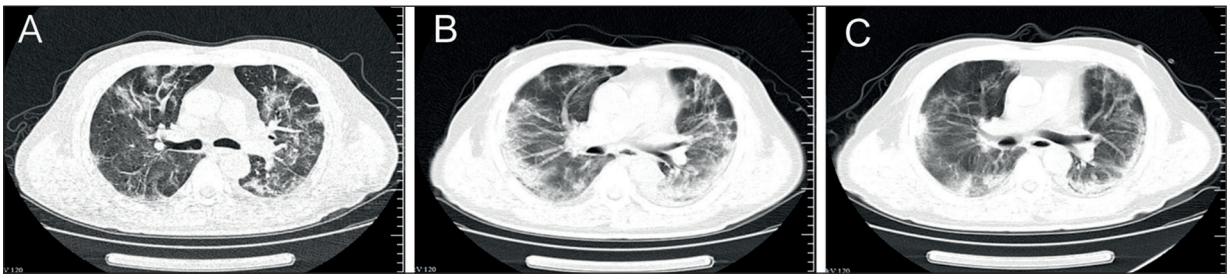

Figure 2. Chest CT images on day 5, day 12 and day 19 of hospitalization. **A,** Chest CT images on day 5 shows ground-glass opacities involving the subpleural regions of both lungs. **B,** Chest CT images on day 12 shows the range of ground-glass opacity extension. **C,** Chest CT images on day 19 shows the range of ground glass opacities assimilated in the bilateral lungs compared with that on day 12.

pleural effusion. Oxygen equipment was changed from a general nasal cannula to HFNC (flow rate 60 L/min), and oxygen saturation fluctuated between 90% and 95%. After 10 hours, the approach was switched to noninvasive ventilation (parameters: S/T mode, IPAP 15 cm H_2O, EPAP 8 cm H_2O, 20 times/min, inspiratory time 1.2 s, FiO_2 70%), with oxygen saturation over 95%. On days 12 through 16 (March 1), the patient's vital signs remained stable; the oxygen pressure in blood gas fluctuated from 60 mmHg to 90 mmHg, while the FiO_2 fluctuated from 50% to 90% on day 12. Laboratory tests showed increased IL-6 (76 pg/ml), CRP (67.5 mg/l), and WBC (10.04×10^9/L); PCT (0.09 μg/L) was normal. On day 16 (March 1), the patient was tested for hepatitis B surface antigen, tuberculosis antibody, and human immunodeficiency virus (HIV) antigen, which were negative. The patient received tocilizumab (Roche, Basel, Switzerland) 400 mg intravenously after multidisciplinary consultation to inhibit the cytokine storm. There were no adverse reactions during the infusion. On day 17 (March 2), the patient felt better. FiO_2 decreased to 50%, and oxygen saturation was maintained over 97%. The patient breathing gradually improved. Noninvasive ventilators, HFNC and nasal catheters were used alternately. On day 19 (March 4), laboratory tests showed that the WBC count (2.75×10^9/L), neutrophil count (1.71×10^9/L), lymphocyte count (0.53×10^9/L), and CRP (9.41 mg/L) declined prominently and that IL-6 (928.8 pg/ml) remarkably increased. Chest CT images revealed the range of ground-glass opacities assimilated in the bilateral lungs compared with that on day 12 (Figure 2C). On day 23(March 8), WBC count (6.07×10^9/L), lymphocyte count (1.20×10^9/L) and CRP (< 3.11 mg/L) were in a normal range, and IL-6 decreased to 469.5 pg/ml. The patient's nasopharyngeal swab specimens were still negative for SARS-CoV-2 nucleic acid; his serum was also negative for the SARS-CoV-2 IgM antibody but positive for the SARS-CoV-2 IgG antibody. The patient was given a test of thyroid function, and the results showed that triiodothyronine (0.58 nmol/L) and tetraiodothyroxine (6.04 pmol/L) declined, while thyroid stimulating hormone (> 46.600 mIU/L), thyroglobulin antibody (26.5 U/ml), and thyroid peroxidase antibody (201.2 U/ml) increased. The patient was considered to have hypothyroidism and received levothyroxine (Ultrale) 50 μg once per day orally. On day 29 (March 14), the patient's noninvasive ventilator time was significantly shortened (3 to 4 hours per day), and his symptoms of dyspnea were significantly alleviated. He could independently go to the bathroom. On day 32 (March 17), the patient was withdrawn from the noninvasive ventilator, and his oxygen saturation was maintained at over 97% under HFNC supplementation. Due to the adjustment of the designated hospital for COVID-19, the patient was transferred to Huoshen Mountain Hospital to continue the treatment and recovery after 10 days.

Discussion

Proinflammatory cytokines have been found in the plasma of COVID-19 patients treated in the intensive care unit (ICU). IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1α (MIP1α) and tumor necrosis factor α (TNF-α) may be significantly increased[4]. Elevated cytokines were also found in patients with Middle East Respiratory

Syndrome (MERS) and Severe Acute Respiratory Syndromes (SARS)[6,7]. On autopsy, inflammatory infiltration of mononuclear cells, mainly lymphocytes, were observed in the bilateral lungs of patients who died of COVID-19[8]. Therefore, some researchers have proposed that a subgroup of patients with severe COVID-19 might have cytokine storm syndrome[9]. Cytokine storms are caused by viruses that induce the body to produce too many cytokines, with an overreaction. Allowing the immune system to react instantly and quickly to kill the virus, it can also cause damage to the blood vessels, organs, tissues and cells, triggering a violent attack on the immune system[10]. It is speculated that cytokine storms cause lung and multiple organ damage, even functional failure, which may be the main reason for the sudden exacerbation of symptoms and death of patients with COVID-19. Thus, inhibiting cytokine storms can be an effective method for treating severe COVID-19 patients[5]. The research team of the First Affiliated Hospital of University of Science and Technology of China analyzed the cytokines involved in the cytokine storm in COVID-19 and found that IL-6 is a key factor. The interleukin-6 receptor blocker tocilizumab is an effective treatment for patients with severe COVID-19, providing a new therapeutic strategy for this fatal infectious disease[11]. A clinical trial study on the safety and effectiveness of tocilizumab in the treatment of COVID-19 has been registered with the Chinese Clinical Trial Registry (Registration No.: ChinCTR2000029765). On March 3, 2020, the National Health and Medical Commission of China launched the New Coronary Virus Pneumonia Diagnosis and Treatment Program (the Seventh Edition) and recommended that severe COVID-19 patients with increased levels of IL-6 could receive tocilizumab for treatment[12]. Tocilizumab is a recombinant human IL-6 monoclonal antibody that specifically binds to soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits IL-6-mediated signal transduction, thereby reducing the inflammatory response. Tocilizumab was approved by the Food and Drug Administration (FDA) of the USA on January 8, 2010, for the treatment of adult patients with moderate to severe active rheumatoid arthritis. It was approved by the FDA of China in March 2013 for the treatment of rheumatoid joints.

The patient's shortness of breath was not severe at the time of admission, but he had a high level of CRP and a low lymphocyte count. His condition deteriorated, and the range of lung lesions increased in 12 days. There were no evident effects of antiviral medicine or methylprednisolone therapy. The case progressed to critical illness because the patient needed oxygen supplementation by a noninvasive ventilator. Before giving tocilizumab, CRP and IL-6 were increased significantly. Tocilizumab was used after excluding tuberculosis, hepatitis B, and HIV infection. The patient's respiratory symptoms gradually improved, avoiding endotracheal intubation and invasive ventilation. In addition to improvement in the blood gas oxygenation index in the auxiliary examination, his CRP level rapidly decreased to a normal level. This result indicates that tocilizumab inhibited the inflammatory response. The patient presented leukopenia on the second day after tocilizumab infusion. It was considered a side effect of tocilizumab and was quickly after corrected by granulocyte colony-stimulating factor. The literature[13] has reported that a side effect of tocilizumab is leukopenia. On the seventh day after tocilizumab infusion, the patient was diagnosed with hypothyroidism according to a thyroid function test. The addition of thyroid globulin and peroxidase antibodies increased, and the patient was considered to have autoimmune thyroiditis. The patient did not have any symptoms of hypothyroidism or thyroiditis, and a thyroid function test was not performed before tocilizumab infusion; thus, it is difficult to determine whether hypothyroidism was a side effect of tocilizumab. Tocilizumab is an IL-6 receptor blocker. When the receptor is blocked, IL-6 might significantly increase in a short period[14]. However, the patient's IL-6 level was greater than the normal upper limit at 2 weeks after tocilizumab infusion. It was unclear what effect the significant increase in IL-6 after tocilizumab infusion had on this patient.

Conclusions

This was a case in which tocilizumab was effective for a critical COVID-19 patient. Although we cannot provide an accurate conclusion about the suitability of tocilizumab for severe COVID-19 patients, which would require clinical registration studies with a large number of severe patients. Clinicians should also consider the side effects of tocilizumab when treating COVID-19 patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

This study was approved by the Wuhan No. 1 Hospital Ethics Committee.

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