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BRIEF DEFINITIVE REPORT

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First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19

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Abstract

Background and Aims: Tocilizumab (TCZ; interleukine-6 receptor antagonist) has been proposed to treat severe forms of Coronavirus disease-19 (COVID-19) because interleukine-6 plays an important role in COVID-19-induced cytokine storm. Several clinical studies have shown very good effects of TCZ in patients with COVID-19, with a few minor side effects reported. Only eight serious liver injuries caused by TCZ were reported before being used in the treatment of patients with COVID-19. Considering the significantly increased use of TCZ for the treatment of COVID-19, we would like to warn of its rare but possible serious hepatotoxicity, especially when used together with other hepatotoxic drugs.

Methods: We describe a patient with COVID-19-induced cytokine storm who developed drug-induced liver injury associated with the use of TCZ.

Results: One day after TCZ administration, serum transaminase levels increased 40-fold. Nevertheless, TCZ had a positive effect on clinical and laboratory parameters in cytokine storm, with transaminases values normalizing in 10 days.

Conclusions: This is the first reported case of DILI caused by TCZ in a COVID-19 patient. Intensive liver function monitoring is imperative in COVID-19 patients, because of frequent polypharmacy with potentially hepatotoxic drugs.

KEYWORDS

COVID-19, drug-induced liver injury, hepatotoxicity, SARS-CoV-2, tocilizumab

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first discovered in Wuhan, China in 2019. The disease it causes (coronavirus disease-19—COVID-19) was officially named on 11 February 2019 by the World Health Organization. At the beginning of May 2020, there are nearly 230 000 cases of COVID-19-related deaths and around 3 267 000 cases confirmed worldwide (WHO: COVID-19 Situation report – 103.) The pathophysiology of COVID-19 includes SARS-CoV-2 binding to the alveolar epithelium, thus activating innate immune system and adaptive immune system and resulting in a pro-inflammatory cascade, including the release of

Abbreviations: ALA, alanine aminotransferase; AST, aspartate aminotransferase; CAR, chimeric antigenic receptor; CIOMS/RUCAM, Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method; COVID-19, coronavirus disease-19; CRP, C-reactive protein; CRS, cytokine release syndrome; DILI, drug-induced liver injury; EASL, European Association for the Study of the Liver; HLA-DR, human leukocyte antigen-DR isotype; ICU, intensive care unit; IL-6, interleukin-6; MSCT, multi-slice computed tomography; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab.

interleukin 6 (IL-6).[1] Elevated levels of IL-6 are predictive of a fatal outcome in COVID-19.[1] Tocilizumab (TCZ) is a humanized recombinant monoclonal antibody that acts as an IL-6 receptor antagonist, specifically binding to soluble or membrane-type IL-6 receptors.[2] In the absence of specific antiviral therapy, the rationale for TCZ use in COVID-19 is based on the understanding that IL-6 plays an important role in COVID-19-induced cytokine storm—cytokine release syndrome (CRS)—characterized by an extreme auto-amplifying cytokine reaction which is followed by the infiltration of inflammatory monocytes/macrophages and lymphocytes into the lung.[2] IL-6-mediated decrease in human leukocyte antigen-DR isotype (HLA-DR) expression causes lymphoid function defects.[2] Severe DILI (drug-induced liver injury) is a very rare complication of TCZ therapy.[3] In this article, we describe the first case of a patient with severe COVID-19 pneumonia who developed DILI associated with the use of TCZ, marked by a 40-fold increase in transaminases levels.

2 | CASE REPORT

On 10 March 2020, a previously healthy 52-year-old man returned from a 1-day business trip from Serbia to Montenegro. Two weeks later, he developed a fever (up to 39.2°C) and a dry cough. He tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) via nasal swab. The patient was admitted to a regional hospital and diagnosed with COVID-19 bilateral pneumonia. He was treated according to the National Health Commission and State Administration of Traditional Chinese Medicine protocol for COVID-19.[4] Twelve days after admission, chest multi-slice computed tomography (MSCT) has shown ground-glass opacities and bilateral basal pulmonary consolidation. He required mechanical ventilation and was transferred to the intensive care unit (ICU).

For the first 4 days of treatment in ICU, the patient was sedated, mechanically ventilated, with stable vital parameters. His treatment included: chloroquine 500 mg twice daily (for the first 12 days before ICU); lopinavir/ritonavir 400/100 mg twice daily (for the first 12 days and 3 days in the ICU); methylprednisolone (60-80 mg daily throughout the ICU treatment); as well as ceftriaxone and azithromycin (throughout the entire treatment).

Six days after admission to the ICU, the patient's condition worsened and the control chest radiography showed the signs of disease progression. In laboratory analyses, C-reactive protein (CRP: 193 mg/L), IL-6 (143 pg/mL), fibrinogen (6.1 g/L), D-dimer (7600 ng/mL) were increased and lymphocyte count was decreased (0.94×10^9/L), aspartate aminotransferase (AST) was in the reference range (30 IU/L), while alanine aminotransferase (ALT) was slightly elevated (83 IU/L). All microbiological analyses (serology on hepatotropic viruses, hemoculture on aerobic and anaerobic bacteria, urine culture) were negative. Based on clinical, radiological and laboratory analyses, he met all the criteria CRS and treatment with TCZ, according to the Chinese[4] and Lombardian[5] protocols. The patient was treated with two doses of TCZ 400 mg (8 mg/kg), with a 12-hour break between doses; continuing with ceftriaxone, azithromycin and methylprednisolone. One day after the patient received both doses of TCZ, acute liver injury (AST 1076 IU/L, ALT 1541 IU/L) was verified in laboratory analyses. Abdominal ultrasound, as well as serum levels of bilirubin, alkaline phosphatase and gamma-glutamyl transferase were normal. According to the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM), he scored 8 points for a 'probable' cause of DILI by TCZ. Also, hepatocellular form of DILI caused by TCZ was diagnosed using the European Association for the Study of the Liver (EASL) guidelines.[6,7] Liver biopsy was not performed to diagnose DILI because of the patient's poor general condition. Several days after TCZ administration, he exhibited clinical improvement with a significant reduction in the levels of acute phase reactants (CRP, IL-6 and D-dimer).

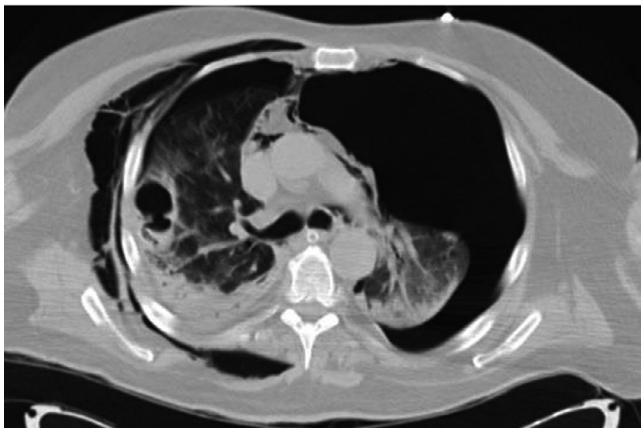

FIGURE 1 Chest multi-slice computed tomography (MSCT) 6 d after administration of tocilizumab. Chest MSCT showed a bilateral pneumothorax and subcutaneous emphysema of the thoracic wall—complications unrelated to the use of tocilizumab, as well as previously described ground-glass opacities and pulmonary consolidation. Comparing the previous MSCT finding, the effect of tocilizumab on the parenchymal recovery of the lungs could not be assessed because of the collapsed lung affected by the pneumothorax

Subsequently, the patient's condition is complicated by bilateral pneumothorax and subcutaneous emphysema (Figure 1). The pneumothorax was treated with drain thoracostomy.

Ten days after the administration of TCZ, transaminase levels, CPR, IL-6 and D-dimer were approaching the normal range (Figure 2). To date, despite the laboratory recovery and the cessation of CRS, his condition is still critical owing to the pulmonary issues.

3 | DISCUSSION

Approximately 5% of patients with COVID-19 require admission to the ICU for severe pneumonia, acute respiratory distress syndrome, rapidly evolving respiratory insufficiency, multi-organ failure or CRS.[8] The pathological immune response depends on the cytokine group (IL-6, IL-2, IL-7, IL-10 and tumour necrosis factor α), but IL-6 is considered to be a major mediator in the pathogenesis of CRS.[1] TCZ

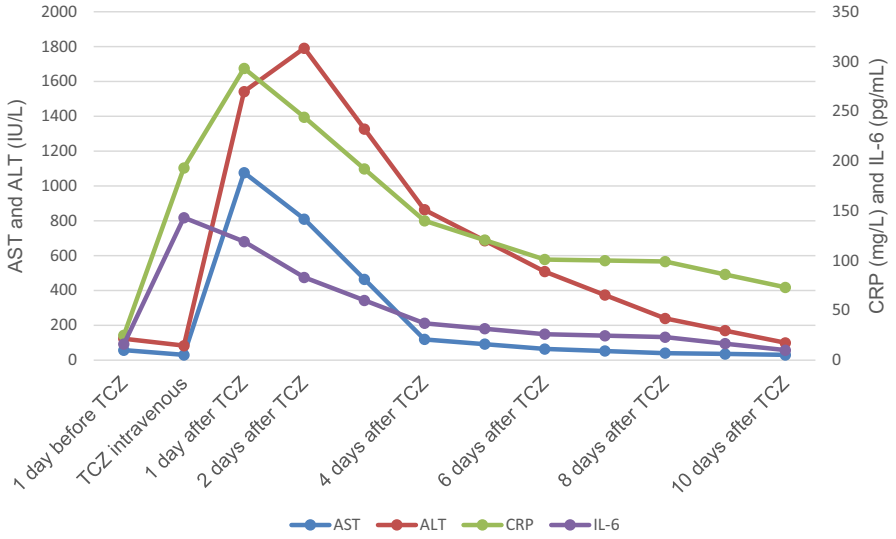

FIGURE 2 Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP) and interleukine-6 (IL-6) in our patient with cytokine release syndrome caused by COVID-19, after the use of tocilizumab (TCZ). Twenty-four hours after tocilizumab administration, transaminase levels increased 40-fold, suggesting a drug-induced liver injury (DILI), but after 10 d, transaminase levels are almost normalized. At the same time CRP and IL-6 levels (laboratory parameters associated with cytokine release syndrome) are approaching to the normal range

is previously approved for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS (very similar syndrome to the CRS in COVID-19).[1] Therefore, in the absence of specific antiviral therapy, TCZ has been included in COVID-19 treatment, with the idea of stopping the progression of systemic inflammation and CRS by blocking IL-6.[5]

Tocilizumab is included in the 7th edition of COVID-19 therapy recommendations issued by the National Health Commission of China.[9] On 13 March 2020, The Lombardy COVID-19 Working Group suggested the following inclusion criteria for off-label TCZ use in COVID-19: the high viral load phase of infection is considered terminated (patient is apyretic for >72 hours and/or at least 7 days have passed since the onset of symptoms); patients suffering from worsening respiratory insufficiency requiring non-invasive ventilation or intubation; as well as patients exhibiting high levels of inflammatory markers (IL-6 >40 pg/mL; D-dimer >1500 ng/mL or rising; elevated CRP, ferritin or fibrinogen).[5] In contrast, their exclusion criteria are as follows: age <18 years; AST/ALT levels more than five times above upper normal; neutrophil and platelet count <500 and <50 000 cells/mmc respectively; documented sepsis from non-SARS-CoV-2 pathogens; complicated diverticulitis or bowel perforation; skin/soft tissue infection; immunosuppressive antirejection therapy; and the presence of co-morbidities linked to an unfavourable outcome (based on the clinical judgement).[5] Liu et al suggested several factors to be taken into account when considering TCZ use in COVID-19: defining diagnosis criteria for CRS in COVID-19 and a disease severity grading system; considering combined antiviral treatment and secondary infection prevention (prophylactic antibiotics, bacteriological and fungal assessments); and cytokine measurement in order to elucidate risk stratification and therapeutic effect monitoring.[10] The treatment presented herein was started with chloroquine and lopinavir/ritonavir, and was changed to TCZ after our patient met all the criteria for CRS (an indication for TCZ) caused by COVID-19.

Several clinical studies have shown very good effects of TCZ on clinical and laboratory parameters in patients with COVID-19, with a few minor side effects reported. A Chinese preprint study on 21 patients with fulfilled criteria for severe COVID-19 (shortness of breath—respiratory rate >30/min, oxygen saturation <93% while resting and PaO2/FiO2 ≤300 mm Hg)—showed that TCZ use caused absorption of pulmonary lesions in 90.5% patients, while body temperature, CRP values and the proportion of peripheral blood lymphocytes returned to normal; no adverse effects were reported.[11] Di Giambenedetto et al reported three cases of COVID-19-related respiratory insufficiency in which TCZ use lead to a rapid relief of respiratory symptoms, resolution of fever and decrease in CRP values, without any reported adverse events.[12] A retrospective study on 15 COVID-19 patients treated in Tongji Hospital in Wuhan (mean age 73 years) showed that IL-6 levels spiked shortly after the introduction of TCZ, afterwards followed by a decrease of IL-6 and acute phase reactants in most patients.[9] The study showed that a positive effect of TCZ is exhibited only after repeated doses in critically ill patients; also, there is no information on TCZ side effects in this study.[9] Morrison et al reported two cases of COVID-19 infection suffering hypertrigliceridaemia after induction of TCZ, one of which had elevated inflammatory biomarkers consistent with acute pancreatitis.[13] The authors hypothesize that TCZ interfered with the role of IL-6 in the free fatty acid uptake to the skeletal muscle.[13] Fontana et al. described the use of TCZ in a COVID-19 kidney transplant recipient, who developed leukopenia with neutropenia as a possible side effect of TCZ; successfully treated with intravenous immunoglobulins.[14]

The most common side effects of TCZ are upper respiratory symptoms, headache and hypertension. Serious side effects are rare: severe infections, acute liver injuries, cytopenia, gastrointestinal ulcerations and perforations.[15] Hepatotoxicity with mild to moderate transaminases elevation is a well-known side effect of TCZ, but severe DILI is very rare complication of TCZ therapy.[3] On 10 December 2019, the Department of Health in Australian Government updated information on TCZ and hepatotoxicity; informing health professionals that eight serious liver injuries had been reported so far, and two of those eight cases required liver transplantation (according to one pharmaceutical company).[16] In most cases, TCZ resulted in severe

hepatic injury when used in combination with other potentially hepatotoxic drugs.[16] Most patients with severe COVID-19 have a history of simultaneous use of multiple drugs that can induce liver injury. In our case, chloroquine treatment was discontinued 6 days before liver injury and antiviral treatment was discontinued 3 days before liver injury. The patient was also treated with a combination of antibiotics, azithromycin and ceftriaxone, in the ICU before hepatic injury occurred.

The incidence of mild liver injury in hospitalized patients with COVID-19 ranges from 14% to 53%, and increased liver enzymes are more commonly observed in men and in more severe cases.[17] Sun et al described several possible mechanisms of liver damage in COVID-19: immune-mediated damage, direct cytotoxicity of SARS-CoV-2 through active viral replication in hepatic cells, anoxia with hypoxic hepatitis, DILI (induced by lopinavir/ritonavir, remdesivir, chloroquine, TCZ, umifenovir etc) and finally reactivation of pre-existing liver disease.[17] Our patient did not have pre-existing liver disease or anoxia leading to liver hypoxia. Slightly elevated transaminase was detected even before acute liver injury, as in most patients with severe COVID-19.

Cai et al reports the results of liver function tests on 417 patients with COVID-19 in Shenzhen, China, concluding that the use of hepatotoxic drugs is the most important risk factor for liver damage.[18] They point out that the use of lopinavir/ritonavir was particularly dangerous and increased the chance of liver damage by four-fold.[18] Searching in the Internet, we did not find any published DILI cases caused by TCZ in a patient with COVID-19. We hypothesize that hepatotoxic effect of TCZ, in our patient, is favoured by previous use of antiviral drugs (lopinavir/ritonavir). Immediately after TCZ administration, serum transaminase levels increased 40-fold. Ten days after the development of DILI, transaminase levels normalized and levels of systemic inflammatory parameters (CRP, IL-6, fibrinogen, D-dimer) simultaneously approached the normal range. According to the EASL guideline for DILI, by calculating the CIOMS/RUCAM score for TCZ, considering the ultrasound examination of the abdomen and analysing the laboratory results, DILI induced by TCZ was a near certainty diagnosis.

In conclusion, this is the first reported case of DILI caused by TCZ in a COVID-19 patient. Simultaneously, TCZ achieved a positive therapeutic effect and led to improvements in clinical and laboratory parameters associated with CRS. Intensive liver function monitoring is imperative in COVID-19 patients, because of frequent polypharmacy with potentially hepatotoxic drugs, especially TCZ. Future studies should aim at the frequency and description of TCZ side effects in COVID-19.

CONFLICT OF INTEREST

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

AUTHOR CONTRIBUTIONS

DM involved in the conception of the study, acquisition of data, drafting of the article and critical revision of the article for important intellectual content. JB and AB involved in acquisition of data and critical revision of the article for important intellectual content. BV involved in acquisition of data and drafting of the article. MR, RL and BS involved in critical revision of the article for important intellectual content.

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REFERENCES

1. Zhao Ming. Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. *Int J Antimicrob Agents*. 2020;105982. doi:10.1016/j.ijantimicag.2020.105982.
2. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe*. 2020:S1931-3128(20)30236-5. doi:10.1016/j.chom.2020.04.009.
3. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Tocilizumab. https://www.ncbi.nlm.nih.gov/books/NBK548243/. Accessed June 18, 2015.
4. National Health Commission & State Administration of Traditional Chinese Medicine. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). 2020. http://www.kankyokansen.org/uploads/uploads/files/jsipc/protocol_V7.pdf. Accessed March 3, 2020.
5. Lombardy Section Italian Society Infectious And Tropical Diseases. Vademecum for the treatment of people with COVID-19. Edition 2.0, 13 March 2020. *Infez Med*. 2020;28(2):143-152.
6. Danan G, Benichou C. Causality assessment of adverse reactions to drugs–I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46(11):1323-1330.
7. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guideline Panel: Chair; Panel members; EASL Governing Board representative: EASL Clinical Practice Guidelines: drug-induced liver injury. *J Hepatol*. 2019;70(6):1222-1261.
8. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the chinese center for disease control and prevention. *JAMA*. 2020;323(13):1239.
9. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol*. 2020:25801. doi:10.1002/jmv.25801.
10. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease, (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun*. 2019;2020:102452. doi:10.1016/j.jaut.2020.102452.
11. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020;117(20):10970-10975.
12. Di Giambenedetto S, Ciccullo A, Borghetti A, et al. Off-label use of tocilizumab in patients with SARS-CoV-2 infection. *J Med Virol*. 2020:25897. doi:10.1002/jmv.25897.
13. Morrison AR, Johnson JM, Ramesh M, Bradley P, Jennings J, Smith ZR. Letter to the Editor: Acute hypertriglyceridemia in patients with COVID-19 receiving tocilizumab. *Journal of Medical Virology*. 2020:25907. doi:10.1002/jmv.25907.
14. Fontana F, Alfano G, Mori G, et al. Covid-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab

and hydroxychloroquine. *Am J Transplant*. 2020. doi:10.1111/ajt.15935.

15. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (Actemra). *Hum Vaccin Immunother*. 2017;13(9):1972-1988.
16. Australian Government Department of Health. Therapeutic Goods Administration. Medicines Safety Update. Update – Tocilizumab and hepatotoxicity, 2019. https://www.tga.gov.au/publication-issue/update-tocilizumab-and-hepatotoxicity. Accessed December 10, 2019.
17. Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int*. 2020. doi:10.1111/liv.14470.
18. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. *J Hepatol*. 2020:S0168-8278(20)30218-X. doi:10.1016/j.jhep.2020.04.006.

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