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Tocilizumab for severe COVID-19 pneumonia: Experience from 5 geriatric Chinese patients with 6 months follow-up

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Abstract

Objective: To enable physicians to understand the efficacy and safety of Tocilizumab (TCZ) in patients with severe coronavirus disease-2019 (COVID-19).
Methods: We respectively reviewed the clinical records, laboratory results, and chest computed tomography (CT) scans of 5 geriatric patients with severe COVID-19 treated with TCZ during their inpatient hospitalization period in Wuhan from February 08, 2020 to April 04, 2020. The survival status of the patients in the third and the sixth month after being discharged was followed up and recorded.
Results: On the fourteenth day after TCZ administration, periphery oxygen saturation rate (SpO_2) returned to normal in 4 patients. The serum Interleukin-6 (IL-6) levels altered in five patients after TCZ infusion. One patient rapidly progressed to acute respiratory distress syndrome (ARDS) and died of multiple organ failures eventually. The other 4 patients were cured and discharged from the hospital. During the inpatient hospitalization period, two patients suffered from virus shedding periods (VSPs) delay, and one patient had mild upper respiratory tract infection. One patient died of esophageal carcinoma one month after being discharged. The other 3 patients survived despite mild cough and insomnia. Serum-specific IgG type antibody titer was decreased in one patient. Six months after being discharged, the other three patients were in good condition.
Conclusion: TCZ may be an efficient therapeutic option for patients with COVID-19. However, the possibility of VSPs delay, secondary infection, serum protective antibody tilter attenuation, and long-term survival status should be addressed before TCZ therapy initiation.

Keywords

coronavirus disease 2019 • interleukin-6 • Tocilizumab • virus shedding periods • follow-up

Introduction

In early December 2019, the coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and spread rapidly across the world. By now, the COVID-19 pandemic has become a worldwide public health challenge.[1] Although most of the patients manifested mild symptoms and had self-limited disease courses, about 25% of patients experienced severe complications such as acute respiratory distress syndrome (ARDS). Moreover, some patients needed close monitoring in the intensive care unit (ICU) and some of them might progress to death.[2] Though numerous therapeutics are currently being tested, there is an urgent need to produce effective therapeutics. Most of the recent researches focused on the development of novel antiviral agents and vaccines.[3]

Accumulating evidence suggests that some patients with severe COVID-19 may suffer from cytokine storm syndromes. Haiming Wei *et al*. identified that the interleukin-6 (IL-6) secreting pathogenic T cells and inflammatory monocytes could incite the cytokine storm, resulting in alveolar capillary blood–gas exchange dysfunction, impaired oxygen diffusion, pulmonary fibrosis, and even organ failure.[4] Tocilizumab (TCZ) is a recombinant humanized anti-human IL-6 receptor monoclonal antibody and binds to the IL-6 receptor with high affinity. TCZ and IL-6 bind to the IL-6 receptor in a competitive manner. Therefore, TCZ could block IL-6 induced immune damage and alleviate the inflammatory responses.[5–7]

Paola *et al*[7] evaluated the efficacy of TCZ in patients with COVID-19. The authors shared their knowledge and experience of TCZ in patients at risk of developing chemokine storm secondary to COVID-19. Nowadays, the efficacy of IL-6 receptor monoclonal antibody-directed therapy on COVID-19 remains equivocal, especially in the aspect of the long-term prognosis. At the very beginning of the COVID-19 outbreak, a multidisciplinary medical team (MDT) including 4 rheumatologists[8, 9] from Beijing Hospital were in charge of an independent inpatient ward to manage the severe COVID-19 patients in the Sino-French New City Branch of Tongji Hospital

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Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

in Wuhan, China. Five geriatric patients took TCZ (Roche Pharma [Schweiz] Ltd.) during their inpatient hospitalization periods. Here we present the clinical and follow up data of 5 patients to facilitate physicians to understand the efficacy and safety of TCZ in COVID-19 management.

Methods

Data Collection

We retrospectively reviewed the medical records of 5 patients with COVID-19 admitted to the inpatient ward of the Sino-French New City Branch of Tongji Hospital in Wuhan from February 08, 2020 to April 04, 2020. The diagnosis of COVID-19 was made according to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission (NHC) of China.[10] All 5 patients were confirmed with SARS-CoV-2 infection by the presence of SARS-CoV-2 ribonucleic acid (RNA) in the nasopharyngeal swab samples detected via the quantitative reverse transcription-polymerase chain reaction (qRT-PCR) method. Two consecutive negative viral test results at least 24 h apart for clearance indicated that the virus was completely cleared.

The clinical characteristics, laboratory and imaging findings, and SARS-Cov-2 Virus shedding periods (VSPs) were reviewed. The VSPs were defined as the time from symptoms onset to the first day of the consecutive negative PCR results before being discharged. All information was obtained and curated with a customized data collection form. The disease severity was defined according to the Chinese management guideline for COVID-19 disease.[10]The acute lung inflammatory lesions in each lobe were assessed based on the extension of lesions in computed tomography (CT) and were semi-quantitively scored as 0 (0%), 1 (1~25%), 2 (26~50%), 3 (51~75%), or 4 (76~100%), respectively. The total imaging severity score (TISS) was calculated by summing up the scores of the five lobes.[11] The TISS in each patient was assessed by two independent physicians (ZC and YJC) and recorded as the average.

The laboratory data included in the present study were peripheral blood white blood cell/neutrophil/lymphocyte counts, serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST)/Albumin/Ferritin/C reactive protein (CRP), and IL-6 levels. The serum IL-6 levels were measured by the electrochemical luminescence method (Roche Diagnostics GmbH). The normal upper ranges of serum CRP, IL-6, and ferritin were 1 mg/L, 7 pg/mL, and 400 μg/L, respectively.

All patients were treated and assessed under the instruction of the Chinese management guideline for COVID-19.[10] The patients would not be discharged until the temperature remained normal for at least 3 consecutive days, and respiratory symptoms ameliorated, and acute exudation lesions in CT were largely absorbed.

The study was approved by the institutional review board of Beijing Hospital (approval number: 2020BJYYEC-083-01).

Statistical Analysis

Statistical analysis was performed with SPSS, version 20.0. Continuous variables were directly expressed as ranges. Categorical variables were expressed as numbers or percentages. The funding agencies neither participated in the study design, data collection, data analysis nor reported the drafting.

Results

Baseline Characteristics of the 5 Patients Treated by TCZ

The 5 patients, including 4 males and 1 female, were all geriatric and had epidemiological histories of SARS-CoV-2 exposure. The age ranged from 66 to 78 years old. All patients had concurrent diseases, such as diabetes, hypertension, and lacunar cerebral infarction. Patient 1 presented with fever, chills, rigor, cough, expectoration, sore throat, myalgia, fatigue, malaise, anorexia, nausea, vomiting, and dyspnea. Patient 2 presented with dyspnea and anorexia. Patient 3 presented with fatigue, myalgia, and malaise. Patient 4 presented with cough, sore throat, chills, fatigue, malaise, and anorexia. Patient 5 presented with myalgia, fatigue, malaise, and anorexia. Laboratory tests showed that all patients had lymphopenia, elevated CRP, IL-6, and ferritin levels. Four out of the five patients had ALT and AST elevation, and serum albumin decrease. Additionally, 4 patients had normal white cell counts and one patient had leucopenia. Pulmonary CT was performed in all patients. The CT results showed typical findings including multiple patches, consolidations, and bilateral ground-glass opacities. The TISS in the 5 patients were 16, 14, 12, 10, and 13, respectively. Before TCZ administration, several kinds of antivirus drugs, such as Lopinavir/Ritonavir, Abidol, and Oseltamivir, *etc.,* were empirically used in the five patients. And moxifloxacin was taken in four out of the five patients. All five patients were considered as severe or critically severe before TCZ administration (Table 1).

The Peripheral SpO_2, Concentration of Oxygen Inhalation, Serum IL-6/CRP Levels of the 5 Patients Before and After TCZ Treatment

Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

Table 1. The baseline of 5 patients treated with TCZ

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
WBC (× 10^9/ L)	3.32	6.3	5.42	6.63	8.98
LC (× 10^9/ L)	0.32	0.42	0.57	0.83	0.76
CRP (mg/L)	49.8	100.2	136.3	160.2	23.7
IL-6 (pg/mL)	72.77	392	74.24	133.4	44.56
Ferritin (μg/L)	1109.6	5380.4	1165.4	768.2	293.3
Past history	Cerebral infarction	Esophageal Carcinoma, Hypertension, and Cerebral infarction	Pulmonary Emphysema and Gallstone	Hypertension and Diabetes	Hypertension and Chronic bronchitis
Severity	Critical	Critical	Severe	Severe	Severe
TISS	16	14	12	10	13
Drugs used before TCZ	Abidol Ribavirin Moxifloxacin	Abidol Oseltamivir	Lopinavir/Ritonavir Moxifloxacin	Abidol TCM* Moxifloxacin	Lopinavir/Ritonavir Oseltamivir Moxifloxacin
TCZ dosages	1	2	2	1	1

*TCZ: Tocilizumab; WBC: White blood count (Normal range: 3.5~9.5× 10^9/L); LC: Lymphocyte count (Normal range: 1.1~3.2× 10^9/L); CRP: C reactive protein (Normal range: <1mg/L); IL-6: Interleukin 6 (Normal range: <7 pg/mL);Ferritin (Normal range: 50~150 μg/L); TISS: Total imaging severity score; *TCM referred to Lianhuaqingwen granules.*

The first dose of TCZ was administrated at 480 mg (proximately 8 mg/kg) intravenously. In cases where the expected responses were not obtained within 72 h, an additional dose of TCZ was given (same dosage as before) according to the physicians' assessment.[4] Specifically, patients 1, 4, and 5 were given one dose of TCZ, patients 2 and 3 were given two doses of TCZ, respectively. Meanwhile, patient 1 was treated with methylprednisolone 80 mg once daily for 4 days, patient 3 was treated with methylprednisolone 40 mg twice daily for 4 days. Except for patient 1, in whom the oxygen therapy was converted from noninvasive nasal catheter to mechanical ventilation, the peripheral SpO_2 returned to normal gradually in the other 4 patients within 7 to 14 days after TCZ infusion. As for the oxygen therapy, the nasal catheter was converted to noninvasive ventilation on the fourth day after TCZ administration and returned to the nasal catheter on the seventh day after TCZ infusion in patient 2. Patient 4 tried a high-flow nasal catheter on the eighth day after TCZ administration but stopped due to intolerance. Patients 3, 4, and 5 experienced continuous oxygen support therapy with a nasal catheter. Eventually, patients 2, 3, 4, and 5 lowered their oxygen support levels with stable SpO_2. The serum CRP levels decreased significantly and remained normal in all patients since the seventh day after TCZ treatment (data was incomplete in one patient). The serum IL-6 levels altered inconstantly in the five patients. The serum IL-6 level decreased gradually after TCZ treatment in one patient. On the contrary, the serum IL-6 levels elevated in short term (day 3) and then decreased gradually (day 4~day 7) after TCZ administration in the other four patients. Thereafter, the serum IL-6 levels transiently surged to a high level due to upper respiratory infection in one patient (after Day 7) and exceeded the detectable upper range in another patient who finally died of multiple organ failure (after Day 7) (Figure 1). The CT scans showed that the lesions were largely absorbed in 4 out of the 5 patients after TCZ administration gradually (Figure 2).

Outcomes

One patient progressed rapidly to ARDS five days after being admitted to ICU and died of multiple organ failure 18 days later. The other 4 patients were cured and discharged from the hospital. VSPs ranged from 12 days to 40 days. In patients 3 and 5, recurrence of positive SARS-CoV-2 viral RNA was detected 14 days since the last negative results. And the viral RNA results turned negative again 5 days later. All 4 patients acquired anti-SARS-CoV-2 IgG antibodies before being discharged. And only one patient suffered from a mild upper respiratory tract infection and was cured quickly after TCZ treatment in the hospital (Table 2).

Survival Status During Follow-up

The four patients who survived during the inpatient hospitalization period were followed up by telephone in the third and the sixth month after being discharged. One patient (Patient 2) died of esophageal carcinoma (Dysphagia,

Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

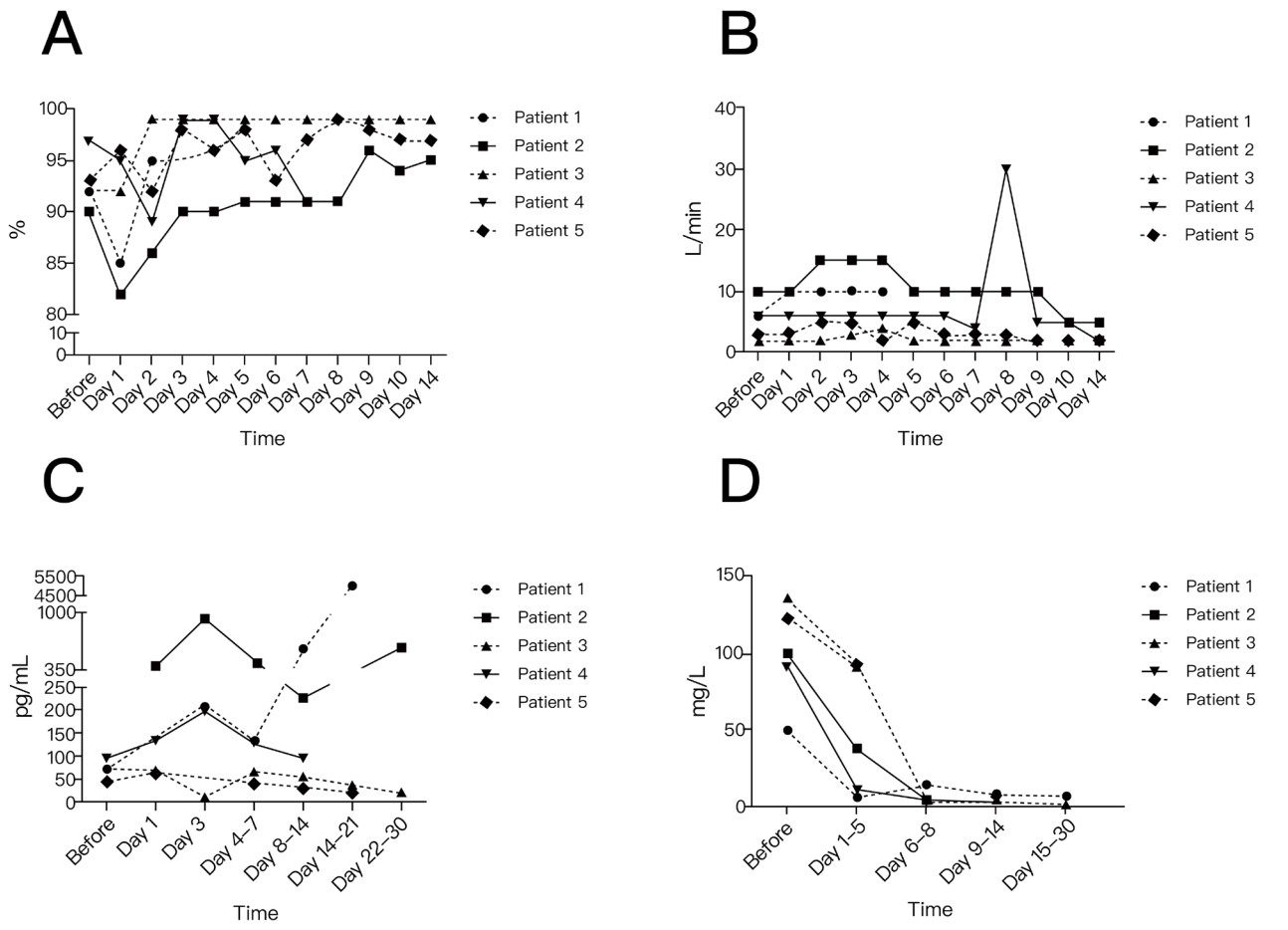

Figure 1. The alteration of SPO_2, concentration of oxygen inhalation, serum IL-6 and CRP levels of the 5 geriatric patients before and after treated by TCZ. A: On the seventh to fourteenth day after treatment, SPO_2 return to normal in 4 patients, only 1 patient (20%) is admitted to ICU. The level of SPO_2 means the lowest level of SPO_2 on the same day; B: All the 5 patients need oxygen therapy at admission. After TCZ treatment, 4 patients lower their oxygen intake, and the oxygen saturations remain stable; and one patient turned to invasive mechanical ventilation; C: The levels of serum IL-6 alter in different ways in the five patients; D: Serum CRP levels decrease significantly after TCZ administration in 5 patients. TCZ: Tocilizumab; SPO_2: Periphery oxygen saturation rate; ICU: Intensive care unit; CRP: C reactive protein 268x206mm (300 x 300 DPI)

hypovolemic shock) one month after being discharged. The other 3 patients lived well. However, two patients had a mild cough, two patients experienced insomnia due to losing their beloved ones, and the other one patient felt being alienated. The inflammatory lesions in CT scans were absorbed in 3 out of the 4 patients. Some ground-glass opacities were left in CT scans in one patient. The SARS-CoV-2 RNA were tested negative in the 3 patients during the COVID-19 census in Wuhan in late May 2020. And anti-SARS-CoV-2 IgG antibody titers were measured again in two patients. The virus-specific IgG type antibodies were maintained in one patient and disappeared in another (Table 3). After the sixth-month follow up, except for one patient who felt being alienated due to COVID-19, the 3 patients were in good condition generally.

Discussion

Recently, therapeutic agents targeting IL-6 modulation are widely used in rheumatic disorders and have become the cornerstone treatment for the management of cytokine release syndrome (CRS) after chimeric antigen receptor (CAR) T cell therapy in hematological malignancies.[12] IL-6 modulation has emerged as a potentially promising option for COVID-19 related ARDS management. In March 2020, the NHC of the People's Republic of China stated that compassionate use may be considered if patients had extensive bilateral lung lesions and increased IL-6 levels.[10] In the meantime, an independent phase II study was announced which evaluated the efficacy and safety of TCZ in the management of COVID-19 related pneumonia from the Italian Medicines Agency. The results

Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

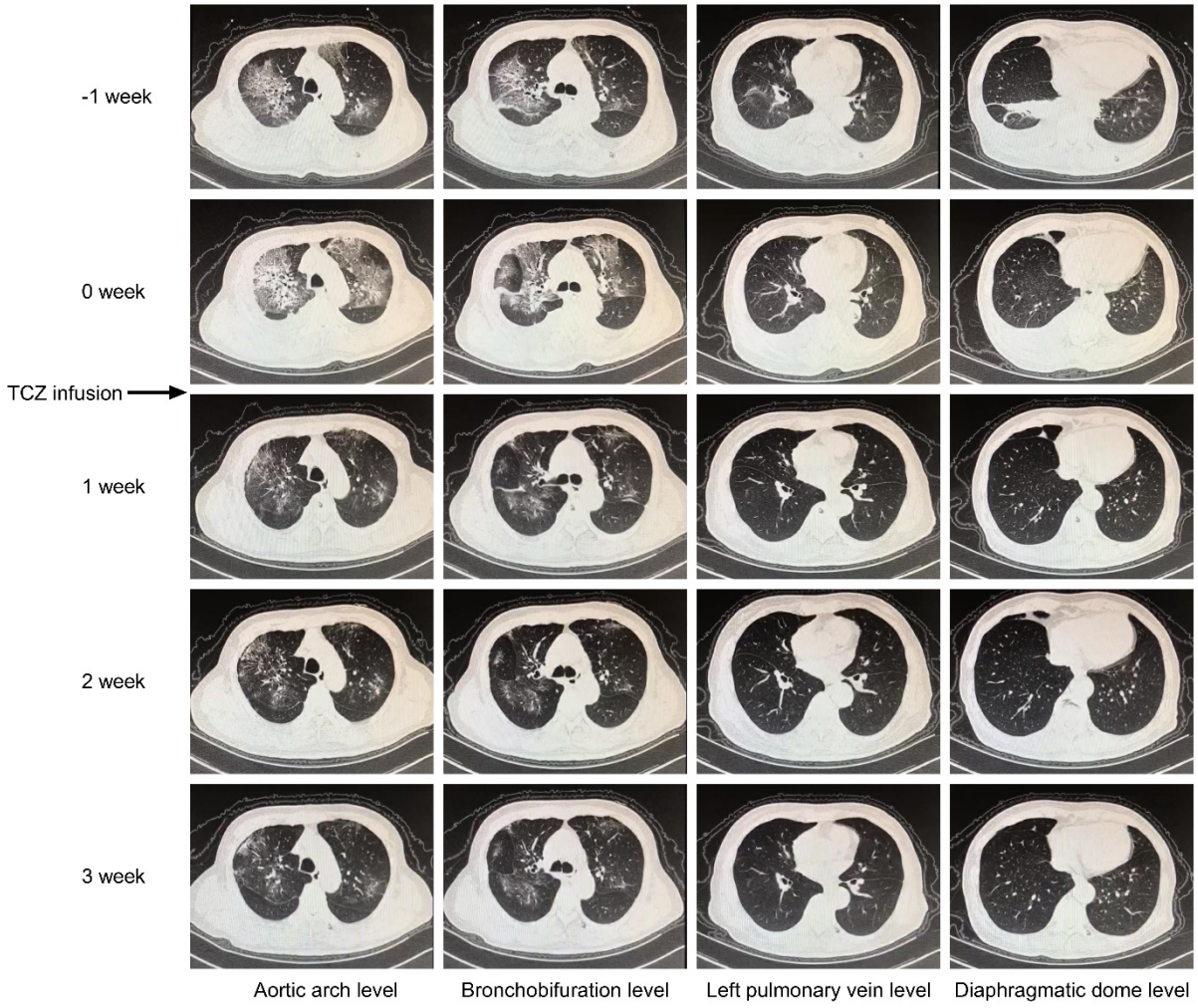

Figure 2. The computed tomography findings of one patient (No.5) before (week -1, 0) and 1, 2, 3 weeks after TCZ administration, respectively. After the comprehensive treatment together with TCZ, the ground-glass opacity lesions were largely absorbed, while some of the fibrosis stripe lesions were left. TCZ: Tocilizumab 268x206 mm (300 x 300 DPI)

showed that TCZ administration was related to rapid and sustained response and significant clinical improvement.[7]

Since then, a large number of observational studies have been carried out throughout the world. In severely ill COVID-19 patients treated with TCZ, the mortality rates were about 25%, ranging from 0% to 39%. And the incidences of secondary infection were about 23% and 41% in severe and critically severe patients, respectively.[13–18] Nowadays, the efficacy of TCZ in COVID-19 management remains unclear. Cumulative evidences with moderate certainty showed that TCZ could reduce the risk of mechanical ventilation in hospitalized COVID-19 patients. Further evidences with low certainty from cohort studies suggested the association between TCZ and lower mortality. However, the results of randomized clinical trials (RCT) showed that TCZ could not reduce short-term mortality. The VSPs and longtime survival status were not observed in these studies due to relatively short follow-up periods.[12]

We presented the clinical and follow-up data of 5 patients who had severe COVID-19 pneumonia and were treated with TCZ. In our study, patients were given TCZ due to rapid progressing lung inflammatory lesions and increasing serum IL-6 levels, which were deemed as parts of pre-clinical or clinical manifestations of CRS.[5] And we hypothesized that patients could benefit from preventing CRS occurring and from blocking CRS. As far as we know, this is the first relative long-term follow-up observational study. In the present study, we found that one patient (20%) died inward. However, the

Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

Table 2.The outcome and adverse effects of 5 patients treated with TCZ during inpatient period

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Discharge from hospital	/	Yes	Yes	Yes	Yes
Transfer to ICU	Yes	None	None	None	None
IMV	Yes	None	None	None	None
LOS (days)	/	37	36	30	37
VSPs (days)	NA	17	40	12	37
Prognosis	Dead	Cured	Cured	Cured	Cured
Cause of death	MOF	/	/	/	/
Anti-COVID-19 IgM (AU/mL)	/	291.56	223.47	24.9	0.75
Anti-COVID-19 IgG (AU/mL)	/	163.58	179.2	224.54	14.7
Secondary infection	None	Yes**	None	None	None
Allergic skin rash	None	None	None	None	None
Liver function damage	None	None	None	None	None
Neutropenia	None	None	None	None	None
Virus Clear delay*	None	None	Yes	None	Yes

*TCZ: Tocilizumab; ICU: Intensive Care Unit; LOS: Length of hospital stay; IMV: Invasive mechanical ventilation VSPs: Virus shedding periods (the duration from disease onset to the first day the consecutive negative PCR); NA: Not available; MOF: Multiple organ failure; IgM: Immunoglobulin M; IgG: Immunoglobulin G; Anti-COVID-19 antibody IgM (Normal range: <10AU/mL);Anti-COVID-19 antibody IgG (Normal range:<10AU/mL). * Virus clear delay means VSPs longer than average (22.09±9.51 days in patients without TCZ treatment during the same inpatient period in unpublished data); **Upper respiratory tract infection.*

Table 3: The survival state of 5 patients at the third month after being discharged

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Remaining symptoms	/	/	None	Cough	Cough and Expectoration
Other symptoms	/	/	Insomnia and alienated	None	Insomnia
Oxygen support	/	/	None	None	None
Survival State	Died of COVID-19	Died of carcinoma	Good	Good	Good
Absorption of lung shadow	/	/	Perfectly	Perfectly	Mostly
SARS-CoV-2 qRT-PCR Recheck	/	/	Negative	Negative	Negative
Anti-COVID-19 antibody IgM	/	/	Negative	Not detected	Negative
Anti-COVID-19 antibody IgG	/	/	Positive	Not detected	Negative

TCZ: Tocilizumab; qRT-PCR: quantitative reverse transcription polymerase chain reaction; IgM: Immunoglobulin M; IgG: Immunoglobulin G

mortality rate in European patients ranged from 0% to 39%. And one patient (20%) suffered from secondary infection which was similar to that in the European patients (about 23%). Our results recorded VSPs delay in 2 (40%) patients, serum protective antibody tilter attenuation in 1 (20%) patient, insomnia in 2 (40%) patients, and cough in 2 (40%) patients, respectively. Although the present study should be interpreted with caution due to its retrospective nature, we believed that our results might help facilitate physicians to better understand the efficacy and outcomes of anti-inflammatory drugs in the management of severe COVID-19.

As far as we know, the most widely used therapeutic option for cytokine storm treatment is by administering corticosteroids. Some researchers surmised that corticosteroids could be used for cytokine storm management induced by the SARS-CoV-2 as well. An open-label study from Wu[19] showed amicable results of corticosteroids in ARDS among

Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

patients with COVID-19 recently. Their study showed that methylprednisolone was related to lower death risks. Among patients with moderate or severe COVID-19 related ARDS, intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in mechanical ventilator-free days.[20] Vulnerable to glucocorticoid-related side effects, i.e., peptic ulcer, hypertension, arrhythmia, *etc.*, elderly patients with severe symptoms were more likely to benefit from biological agents targeting vital cytokines in the inflammatory storm. Therefore, we proposed that TCZ administration should be initiated in patients who were vulnerable to glucocorticoid-related side effects.

Because of the relatively high costs and the unfavorable results in RCTs, the indication and time for TCZ infusion should be thoroughly studied before being widely used for COVID-19 management. IL-6 per se has context-dependent pro- and anti-inflammatory properties and is now regarded as a bulge target for clinical intervention.[12] According to the previous murine studies, IL-6 is essential for the control of disease progression in the early stages of other infections. Thus, the proper initiation time of drugs targeting the IL-6 pathway might be the most important factor in COVID-19 management.[21] Patients with high fever (39°C) were more likely to have ARDS in COVID-19. Therefore, high fever in the early stage of COVID-19 was listed as an inclusion criterion in some RCTs.[22] Moreover, IL-6 was regarded as the vital factor in the pathogenesis of severe disease of COVID-19. In a meta-analysis, the mean serum IL-6 levels were 56.8 pg/mL and 17.3 pg/mL in patients who had severe and mild COVID-19, respectively. Accordingly, severe patients with serum IL-6 levels higher than 56.8 pg/mL might be more suitable for receiving IL-6 receptor antagonist therapy.[23] However, as IL-6 levels were not routinely tested in most hospitals, CRP served as a surrogate marker for IL-6 in some RCTs (RCT-TCZ-COVID-19: NCT04346355).[22] Indeed, the two parameters were not consistently parallel, which might partly account for the unsatisfactory results of TCZ in the treatment of severe COVID-19 in RCTs.

In conclusion, we retrospectively observed the efficacy and safety of TCZ in 5 geriatric patients with severe and critical COVID-19. Except for one patient who died during the inpatient hospitalization period, the other four patients gradually recovered and were discharged from the hospital. Another patient died of esophageal carcinoma one month after being discharged and the rest three patients were in good condition at the sixth month after being discharged. As a promising therapeutic for COVID-19, the indication, proper time point, the possibility of VSPs delay and secondary infection should be thoroughly considered before TCZ initiation.

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Author contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. YC, AL, and ZC had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. AL, YC, XW, MG, and CH designed this study initially.

Competing interests

None declared.

Ethics approval

The study was approved by the institutional review board of Beijing Hospital

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Original Article • DOI: 10.2478/rir-2021-0009 • 2(1) • 2021 • 35–42

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